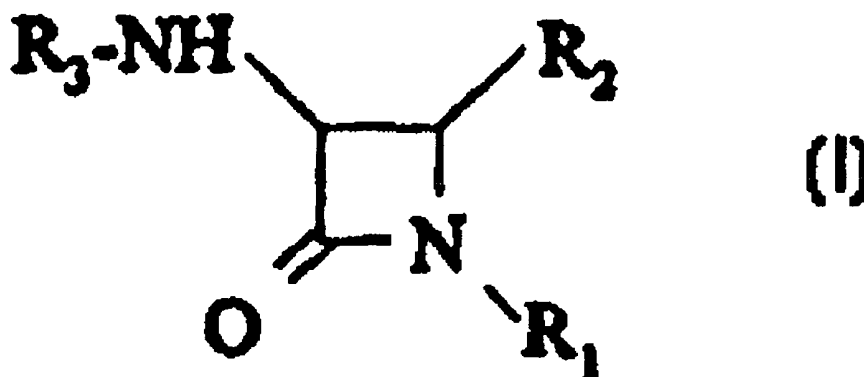


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(54) **DERIVES D'AZETIDINE-2-ONE DISUBSTITUEE EN 3,4**
REGULATEURS DE CYSTEINE PROTEINASE
(54) **3,4-DISUBSTITUTED AZETIDIN-2-ONE DERIVATIVES**
USEFUL AS CYSTEINE PROTEINASE REGULATORS



(57) Certains dérivés d'azétidine-2-one disubstituée en 3,4 exercent une excellente inhibition de cystéine protéinase, et on peut les utiliser pour le traitement de différentes maladies, à savoir par exemple: myopathie musculaire progressive, infarctus du myocarde, résorption osseuse, arthrite, métastases cancéreuses, emphysème pulmonaire, choc septique, ischémie cérébrale, fonction mnésique, maladie d'Alzheimer et cataracte, paludisme, dégradation de la membrane basale des capillaires du glomérule rénal, infection bactérienne, maladies inflammatoires, maladies parasitaires, et infections virales. On décrit les dérivés susmentionnés, représentés par la formule (I), dans laquelle R₁, R₂ et R₃ sont tels que définis, ou bien un sel pharmaceutiquement acceptable de ces dérivés.

(57) The present invention is based on the discovery that certain 3,4-disubstituted-azetidin-2-one derivatives exhibit excellent cysteine proteinase inhibitory activity which can be used for treatment of different diseases such as muscular dystrophy, myocardial infarction, bone resorption, arthritis, cancer metastasis, pulmonary emphysema, septic shock, cerebral ischemia, memory function, Alzheimer and cataract, malaria, glomerular basement membrane degradation, bacterial infection, inflammatory diseases, parasitic infections, and viral infections. In accordance with the present invention, there is provided a 3,4-disubstituted-azetidin-2-one derivatives of formula (I), wherein R₁, R₂ and R₃ are as defined herein, or a pharmaceutically acceptable salt thereof.

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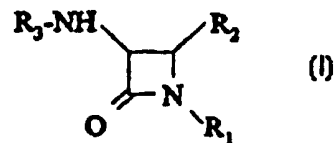
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(54) Title: 3,4-DISUBSTITUTED AZETIDIN-2-ONE DERIVATIVES USEFUL AS CYSTEINE PROTEINASE REGULATORS

(57) Abstract

The present invention is based on the discovery that certain 3,4-disubstituted-azetidin-2-one derivatives exhibit excellent cysteine proteinase inhibitory activity which can be used for treatment of different diseases such as muscular dystrophy, myocardial infarction, bone resorption, arthritis, cancer metastasis, pulmonary emphysema, septic shock, cerebral ischemia, memory function, Alzheimer and cataract, malaria, glomerular basement membrane degradation, bacterial infection, inflammatory diseases, parasitic infections, and viral infections. In accordance with the present invention, there is provided a 3,4-disubstituted-azetidin-2-one derivatives of formula (I), wherein R₁, R₂ and R₃ are as defined herein, or a pharmaceutically acceptable salt thereof.



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3,4-Disubstituted Azetidin-2-one Derivatives Useful
as Cysteine Proteinase Regulators

This application claims priority of United States Provisional patent application Serial Number 60/026,516, filed September 23, 1996.

5 Background of the Invention

Cysteine proteinases containing a highly reactive cysteine residue with a free thiol group at the active site have been known as playing an important role in certain conditions distinguished by aberrant protein turnover such as: muscular dystrophy (Am. J. Pathol. 1986, 122, 193-198; Am. J. Pathol. 1987, 127, 461-466), myocardial infarction (J. Am. Coll. Cardiol. 1983, 2, 681-688), bone resorption (Biochem. J. 1991, 279, 167-274; J. Biol. Chem. 1996, 271, 2126-2132; and Biochem. Biophys. Acta 1992, 1116, 57-66), arthritis (Arthritis Rheumatism 1994, 37, 236-247; and Biochem. Pharmacol. 1992, 44, 1201-1207), cancer metastasis (Cancer Metastasis Rev. 1990, 9, 333-352), pulmonary emphysema (Am. Rev. Respir. Dis. 1975, 111, 579-586), septic shock (Immunol. Today 1991, 11, 404-410, Biochemistry 1994, 33, 3934-3940), cerebral ischemia, memory function, Alzheimer and cataract (TIPS 1994, 15, 412-419, Bioorg. Med. Chem. Lett. 1995, 4, 387-392, Proc. Natl. Acad. Sci. USA 1991, 88, 10998-11002), malaria (J. Med. Chem. 1995, 38, 5031-5037), glomerular basement membrane degradation (Biochem. Bioph. Acta 1989, 990, 246-251), bacterial infection (Nature 1989, 337, 385-386), inflammatory diseases (Protein Science 1995, 4, 3-12), parasitic infections (Annu. Rev. Microbiol. 1993, 47, 821-853; Parasitol. Today 1990, 6, 270-275), and viral infections (Biochem. 1992, 31, 7862-7869).

25 A variety of cysteine proteinase have been shown to be present in mammalian tissue. The most notable of these proteinase are the lysosomal cathepsins (cathepsin B, H, S, K and L) and the cytoplasmic Ca²⁺ dependent enzymes, the calpains. These enzymes are, therefore, excellent targets for the development of specific inhibitors as possible therapeutic agents.

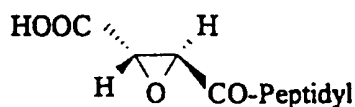
30 Cysteine proteinase are inhibited by several types of peptide derived inhibitors such as peptidyl aldehyde (Eur. J. Biochem. 1982, 129, 33-41), chloromethyl ketone (Acta. Biol. Med. Ger. 1981, 40, 1503-1511), diazomethyl

ketone (Biochemistry 1977, 16, 5857-5861), monofluoromethyl ketone (Biochemical Pharmacology 1992 44, 1201-1207), acyloxy methyl ketone (J. Med. Chem. 1994, 37, 1833-1840), O-acyl hydroxamates (Biochem. Biophys. Research Communications 1988, 155, 1201-1206), methyl sulphonium salts (J. Biol. Chem. 1988, 263, 2768-2772) and epoxy succinyl derivatives (Agric. Biol. Chem. 1978, 42, 523-527) without significantly inhibiting other classes of proteinases.

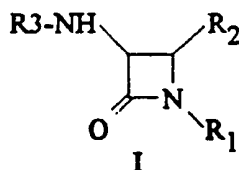
Unfortunately, the effectiveness in vivo of such compounds is not as much as expected on the basis of in vitro inhibitory activity, and there exists a continuing need to develop new cysteine proteinase inhibitors with high selectivity and lower toxicity.

Peptidyl-CO-Y

Y = H, CH₂Cl, CHN₂, CH₂F,
CH₂OCOAr, NHOCOR,
CH₂S-(CH₃)₂



Epoxysuccinyl derivative

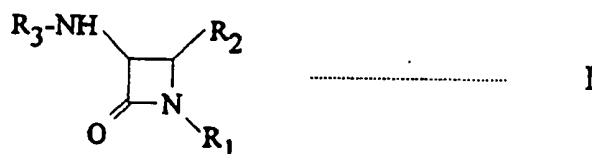


Our laboratory has been actively involved in search of novel types of cysteine proteinase inhibitors with high selectivity among cysteine proteinase class of enzymes. We have found that a novel class of compounds having natural peptidyl group at C-3 of reactive group 3-amino-4-substituted azetidin-2-one, represented by formula I, exhibit an excellent cysteine proteinase regulatory (e.g., inhibitory) activity and selectivity among cysteine proteinases, which is reported in US patent application no.08/415,055.

Summary of the Invention

In accordance with the present invention, there are provided 3,4-disubstituted azetidin-2-one derivatives which exhibit excellent cysteine proteinase regulatory activity and which can be used for treatment of different diseases such as muscular dystrophy, myocardial infarction, bone resorption, arthritis, cancer metastasis, pulmonary emphysema, septic shock, cerebral ischemia, memory function, Alzheimer and cataract, malaria, glomerular basement membrane degradation, bacterial infection, inflammatory diseases, parasitic infections, and viral infections.

In accordance with the present invention, there are provided 3,4-disubstituted azetidin-2-one derivatives of formula I and pharmaceutically acceptable salts thereof:



wherein

R_1 is

hydrogen; or

$-SO_3^+M^+$ wherein M is a hydrogen atom, a metal ion which is selected from sodium, potassium, magnesium, and calcium, or $N^+(R_4)_4$ wherein R_4 is a C_1 - C_6 alkyl group.

R_2 is

(a) a group $-OCOR_5$ wherein R_5 is

(i) a C_1 - C_6 alkyl group,

(ii) a C_2 - C_6 alkenyl group,

(iii) a C_2 - C_6 alkynyl group,

(iv) a C_3 - C_6 cycloalkyl group,

(v) a phenyl group,

(vi) a naphthyl group, or

(vii) a monocyclic or bicyclic heterocyclic group,

which group (i), (ii), (iii), (iv), (v), (vi), or (vii) is unsubstituted or substituted by 1, 2 or 3 substituents independently selected from

hydroxy,

halogen,

carboxy,

C₁-C₄ alkyl (which is unsubstituted or substituted at least once with carboxy and/or amino),

C₁-C₂ alkoxy,

amino,

cyano, and

phenyl and monocyclic or bicyclic heterocyclic groups, which phenyl and heterocyclic groups are unsubstituted or substituted by 1 or 2 substituents independently selected from

hydroxy,

halogen,

carboxy,

C₁-C₄ alkyl,

C₁-C₂ alkoxy,

amino, and

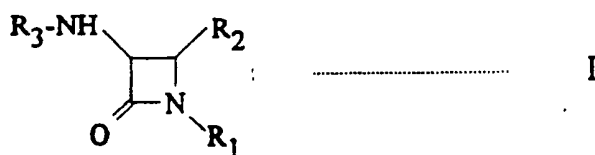
cyano;

or (b) a group -XR₅ wherein X is selected from the group consisting of O, S, SO, and SO₂, and R₅ is as defined above;

R₃ is selected from the group consisting of D- or L-phenyl glycine, D- or L-t-butyl alanine, D- or L-homophenyl alanine, D- or L-pyridyl alanine, D- or L-thienyl alanine, D- or L-naphthyl alanine, D- or L-methoxy phenyl alanine, D- or L-halo phenyl alanine, D- or L-ε-nitro arginine, D- or L-citrulline, D- or L-2-indoline carboxylic acid, D- or L-cycloalkyl glycine (e.g., cyclopentyl glycine), D- or L-4-hydroxy-3-nitro-phenylalanine, D- or L-4-amino-3,5-diiodo-phenylalanine, D- or L-4-hydroxy-3,5-diiodo-phenylalanine, D- or L-β-(3-benzothienyl)-alanine, D- or L-3,4(methylenedioxy)phenylalanine, D- or L-3,4(ethylenedioxy)phenylalanine,

D- or L-4,4'-biphenylalanine, D- or L-3,4-dichlorophenylalanine, D- or L-4-iodophenylalanine, D- or L-4-nitrophenylalanine, D- or L-pentafluorophenylalanine, D- or L-4-thiazolylalanine, D- or L-3-trifluoromethylphenylalanine, D- or L-4-trifluoromethylphenylalanine, D- or L-3-sulfamoyl-alanine, D- or L-t-butyloxy alanine, D- or L-1-t-butyloxymethylalanine, D- or L-trimethylalanine, D- or L-3,4-diisopropoxyphenylalanine, D- or L-propyl alanine, and D- or L-ethyl alanine, in which the NH_2 of any of the above groups is unsubstituted or substituted once or twice with R_7 wherein R_7 is $-\text{COOR}_5$, $-\text{COR}_5$, $-\text{SO}_2\text{R}_5$, or $-\text{COR}_{14}$ wherein R_5 is as defined above and R_{14} is amino group which is unsubstituted or substituted at least once with C_1 - C_6 alkyl group which is unsubstituted or substituted at least once with 1 or 2 substituents selected from hydroxy, halogen, cyano, amino, heterocycle, and phenyl (wherein the heterocycle or phenyl is unsubstituted or substituted at least once by 1 or 2 substituents selected from halogen, hydroxy, cyano, carboxy and amino).

In a preferred aspect of the present invention, there are provided 3,4-disubstituted azetidin-2-one derivatives of formula I and pharmaceutically acceptable salts thereof:



20 wherein

R_1 is

hydrogen; or

$-\text{SO}_3\text{M}^+$ wherein M is a hydrogen atom, a metal ion which is selected from sodium, potassium, magnesium, and calcium, or $\text{N}^+(\text{R}_4)_4$

25 wherein R_4 is a C_1 - C_6 alkyl group.

R_2 is

$-\text{OCOR}_5$ wherein R_5 is (i) a C_1 - C_6 alkyl group which is unsubstituted or substituted at least once by 1 or 2 substituents selected from

hydroxy, halogen, and amino, or (ii) a phenyl group which is unsubstituted or substituted at least once by 1-3 substituents selected from hydroxy, halogen, C₁-C₄ alkyl group, C₁-C₂ alkoxy group, and cyano; or

-XR₆ wherein X is O, S, SO, or SO₂; R₆ is (i) a C₁-C₆ alkyl group which is unsubstituted or substituted at least once by 1 or 2 substituents selected from hydroxy, halogen, amino and phenyl (ii) a C₃-C₆ cycloalkyl group, (iii) a phenyl group which is unsubstituted or substituted at least once by 1-3 substituents selected from hydroxy, halogen, carboxy, C₁-C₄ alkyl group (which is unsubstituted or substituted with carboxy, amino or both), C₁-C₂ alkoxy group, cyano and heterocycle group, or (iv) naphthyl group which is unsubstituted or substituted at least once by 1-3 substituents selected from hydroxy, halogen, carboxy, C₁-C₄ alkyl group (which is unsubstituted or substituted at least once with carboxy, amino or both), C₁-C₂ alkoxy group and cyano;

R₃ is selected from α -amino acid residues of α -amino acids, the NH₂ of which is unsubstituted or substituted once or twice with R₇ as defined below. The term "amino acid residue" used herein refers to the remaining group after the removal of the hydroxy group from a carboxy group of an amino acid. According to the present invention, the α -amino acid can be selected from the group consisting of: D- or L-phenyl glycine, D- or L-t-butyl alanine, D- or L-homophenyl alanine, D- or L-pyridyl alanine, D- or L-thienyl alanine, D- or L-naphthyl alanine, D- or L-methoxy phenyl alanine, D- or L-halo phenyl alanine, D- or L- ϵ -nitro arginine, D- or L-citrulline, D- or L-2-indoline carboxylic acid, D- or L-cycloalkyl glycine (e.g., cyclopentyl glycine), D- or L-4-hydroxy-3-nitro-phenylalanine, D- or L-4-amino-3,5-diiodo-phenylalanine, D- or L-4-hydroxy-3,5-diiodo-phenylalanine, D- or L-4-hydroxy-3,5-dibromo-phenylalanine, D- or L- β -(3-benzothienyl)-alanine, D- or L-3,4(methylenedioxy)phenylalanine, D- or L-3,4(ethylenedioxy)phenylalanine, D- or L-4,4'-biphenylalanine, D- or L-3,4-dichlorophenylalanine, D- or L-4-iodophenylalanine, D- or L-4-nitrophenylalanine, D- or L-pentafluorophenylalanine, D- or L-4-thiazolylalanine, D- or L-3-trifluoromethylphenylalanine, D- or L-4-trifluoromethylphenylalanine, D- or L-

3-sulfamoyl-alanine, D- or L-t-butyloxy alanine, D- or L-1-t-butyloxymethylalanine, D- or L-trimethylalanine, D- or L-3,4-diisopropoxyphenylalanine, D- or L-propyl alanine, and D- or L-ethyl alanine, in which the NH_2 of any of the above groups is unsubstituted or substituted

5 once or twice with R_7 wherein R_7 is

- COOR_8 wherein R_8 is a C_1 - C_6 alkyl group which is unsubstituted or substituted at least once with phenyl group,

- COR_9 wherein R_9 is

(i) a C_1 - C_6 alkyl group which is unsubstituted or substituted at
10 least once by 1 or 2 substituents selected from hydroxy, halogen, cyano, amino, heterocycle, or phenyl (wherein the heterocycle or phenyl is unsubstituted or substituted at least once by 1 or 2 substituents selected from halogen, hydroxy, cyano, carboxy and amino); (ii) a heterocycle which may be mono or bicyclic or (iii) amino group which is unsubstituted or substituted at
15 least once with C_1 - C_6 alkyl group which is unsubstituted or substituted at least once with 1 or 2 substituents selected from hydroxy, halogen, cyano, amino, heterocycle, and phenyl (wherein the heterocycle or phenyl is unsubstituted or substituted at least once by 1 or 2 substituents selected from halogen, hydroxy, cyano, carboxy and amino); or

20 SO_2R_{10} wherein R_{10} is

(i) a C_1 - C_6 alkyl group (ii) a C_2 - C_4 alkenyl group which is unsubstituted or substituted at least once with heterocycle or phenyl, or (iii) a phenyl group which is unsubstituted or substituted at least once by 1-3 substituents selected from hydroxy, halogen, carboxy, C_1 - C_4 alkyl group, C_1 -
25 C_2 alkoxy group and cyano.

The pharmaceutically acceptable salts of formula I are selected from salts of sodium, potassium, magnesium, calcium, hydrogen chloride, tartaric acid, succinic acid, fumaric acid or p-toluenesulfonic acid.

Examples of C_1 - C_6 alkyl group as substituents in R_4 , R_5 , R_6 , R_8 , R_9 , or
30 R_{10} are straight or branched chain alkyl group having 1-6 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylprop-1-yl, 2-methylprop-2-yl, pentyl, 3-methylbutyl, hexyl and the like.

Examples of halogen atoms as substituents in R_5 , R_6 , R_9 , or R_{10} are fluorine, chlorine, bromine or iodine.

Examples of C_2 - C_6 alkenyl group as defined in R_5 and R_{10} are alkenyl group having 2-4 carbon atoms such as ethenyl, 1-propenyl, 2-propenyl, 1-
5 butenyl, 3-butenyl and the like.

Examples of C_2 - C_6 alkynyl group as defined in R_5 and R_{10} are alkynyl group having 2-4 carbon atoms such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 3-butynyl and the like.

Examples of C_3 - C_6 cycloalkyl group as defined in R_5 and R_6 are
10 cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

As used herein "monocyclic heterocyclic" means a 5- or 6-membered aromatic or non-aromatic heterocyclic group containing 1, 2, 3 or 4 heteroatoms selected from O, S or N; and "bicyclic heterocyclic" means a monocyclic heterocyclic as defined above which is fused to a second 5- or 6-
15 membered carbocyclic or 5- or 6-membered heterocyclic ring.

Examples of preferred heterocyclic group or substituent as defined in R_5 , R_6 , R_9 , or R_{10} include C_2 - C_{11} mono or bicyclic heterocyclic group which may have 1-3 heteroatoms selected from nitrogen, sulphur or oxygen such as thiophene, pyridine, 1,2,3-triazole, 1,2,4-triazole, quinoline, benzofuran,
20 benzothiophene, morpholine, thiomorpholine, piperazine, piperidine and the like.

Examples of C_1 - C_6 alkyl group as substituents in R_5 , R_6 , R_9 , or R_{10} are methyl, ethyl, propyl, 2-methyl propyl, butyl, 1,1-dimethyl ethyl and the like.

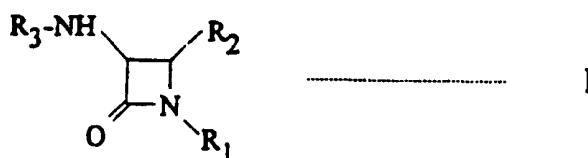
Examples of C_1 - C_2 alkoxy group as substituents in R_5 , R_6 , R_9 , or R_{10}
25 are methoxy or ethoxy.

The term "amino acid residue" used herein refers to the remaining group after the removal of the hydroxy group from a carboxy group of an amino acid.

The azetidinone nucleus carries two asymmetric carbon atoms at
30 position 3 and 4, and can exist as 4-diastereoisomers. In general, the preferred isomer is that in which the hydrogen atoms at C3 and C4 are cis to each other for superior inhibitory activity against different cysteine proteinase

such as papain, Cathepsin B and Cathepsin L. Such diastereoisomers and their racemic mixtures are also included within use of the azetidinone derivatives as cystein proteinase inhibitor.

In accordance with preferred embodiments of the invention, there are provided 3,4-disubstituted-azetidin-2-one derivatives of formula I.



Wherein:

R_1 is selected from hydrogen, or sulphonic acid;

R_2 is selected from acetoxy, butyloxy, 2-carboxy ethyloxy, 2-aminoethyloxy, 2-fluoro ethoxy, cyclopentyloxy, cyclohexyloxy, cyclohexylthio, phenoxy, methyl phenoxy, naphthyloxy, morpholino phenyloxy, 2-hydroxy ethylthio, phenylthio, phenylsulphonyl, 4-(2-carboxy-2-amino ethyl)-phenoxy, 4-carboxy phenoxy, 3-carboxy phenoxy, 2-pyridylthio, 4-pyridylthio, benzyloxy and the like;

R_3 is selected from 1-benzyloxycarbonyl-2-indoline carboxylic acid, N-benzyloxy carbonyl phenyl glycine, N-benzyloxy carbonyl homophenyl alanine, N-benzyloxy carbonyl pyridyl alanine, N-benzyloxy carbonyl thienyl alanine, N-benzyloxy carbonyl naphthyl alanine, N-benzyloxy carbonyl halophenyl alanine, N-benzyloxy carbonyl naphthyl alanine, N-(3-phenyl propanoyl) naphthyl alanine, N^ε-nitro arginine, N-(3-phenyl propanoyl) citrulline, N-benzylamino carbonyl naphthyl alanine, N-(2-phenyl-eth-1-en-sulphonyl)-naphthyl alanine, N-benzyloxycarbonyl-t-butyloxyalanine; N-benzyloxycarbonyl-t-butyloxymethyl alanine; N-benzyloxycarbonyl-t-butyl alanine; N-phenylpropionoyl-t-butyl alanine; N-phenylpropionoyl-trimethyl alanine; N-phenylpropionoyl-(3, 4-dimethoxyphenyl) alanine; N-phenylpropionoyl-(3,4-ethylenedioxyphenyl) alanine; N-benzyloxycarbonyl-3-benzothienyl alanine; N-benzyloxycarbonyl-(4,4'-biphenyl) alanine; N-

benzyloxycarbonyl-(2-chlorophenyl)alanine; N-benzyloxycarbonyl-(4-chlorophenyl)alanine; N-benzyloxycarbonyl-(3,4-dichloro)-phenylalanine; N-benzyloxycarbonyl-(diphenyl) alanine; N-benzyloxycarbonyl-(2-fluoro) phenylalanine; N-benzyloxycarbonyl-(4-fluoro-phenyl) alanine; N-benzyloxycarbonyl-(3,4-difluoro-phenyl) alanine; N-benzyloxycarbonyl-(4-iodo-phenyl) alanine; N-benzyloxycarbonyl-2-(naphthyl) alanine; N-benzyloxycarbonyl-(4-nitro-phenyl) alanine; N-benzyloxycarbonyl-(pentafluorophenyl) alanine; N-benzyloxycarbonyl-(4-thiazolyl) alanine; N-benzyloxycarbonyl-3-(trifluoromethylphenyl) alanine; N-benzyloxycarbonyl-4-(trifluoromethylphenyl) alanine; N-benzyloxycarbonyl-(3-sulfamoyl) alanine; N-phenylpropionoyl-(3,4-methylenedioxyphenyl) alanine; N-phenylpropionoyl-(3,4-diisopropoxyphenyl) alanine; N-benzyloxycarbonyl-propyl alanine; and N-benzyloxycarbonyl-ethyl alanine.

More specifically, the most preferred embodiments of the present invention include the following compounds:

(3S,4S)-3-(1-N-benzyloxycarbonyl-2-indolinecarbonyl)-amino-4-acetoxy-azetidin-2-one;

(3S,4S)-3-(N-benzyloxycarbonyl-D-phenylglycyl)-amino-4-acetoxy-azetidin-2-one;

(3S,4S)-3-(N-benzyloxycarbonyl-DL-phenylglycyl)-amino-4-acetoxy-azetidin-2-one;

(3S,4S)-3-(N-benzyloxycarbonyl-L-homophenylalanyl)-amino-4-acetoxy-azetidin-2-one;

(3S,4S)-3-(N-benzyloxycarbonyl- β -(3-pyridyl)-L-alanyl)-amino-4-acetoxy-azetidin-2-one;

(3S,4S)-3-(N-benzyloxycarbonyl- β -(2-pyridyl)-L-alanyl)-amino-4-acetoxy-azetidin-2-one;

(3S,4S)-3-(N-benzyloxycarbonyl- β -(2-thienyl)-DL-alanyl)-amino-4-acetoxy-azetidin-2-one;

(3S,4S)-3-(N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl)-amino-4-acetoxy-azetidin-2-one;

(3S,4S)-3-(N-benzyloxycarbonyl- β -(3-fluorophenyl)-L-alanyl)-amino-4-

- acetoxy-azetidin-2-one;
(3S,4S)-3-{N-benzyloxycarbonyl- β -(4-methoxyphenyl)-L-alanyl}-amino-4-acetoxy-azetidin-2-one;
(3S,4S)-3-{N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl}-amino-4-
5 phenoxy-azetidin-2-one;
(3S,4S)-3-{N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl}-amino-4-(3-methyl phenoxy)-azetidin-2-one;
(3S,4R)-3-{N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl}-amino-4-(3-methyl phenoxy)-azetidin-2-one;
10 (3S,4S)-3-{N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl}-amino-4-(2-naphthoxy)-azetidin-2-one;
(3S,4R)-3-{N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl}-amino-4-(2-naphthoxy)-azetidin-2-one;
(3S,4S)-3-{N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl}-amino-4-{3-
15 (morpholin-4-yl)-phenoxy}-azetidin-2-one;
(3S,4R)-3-{N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl}-amino-4-{3-(morpholin-4-yl)-phenoxy}-azetidin-2-one;
(3S,4SR)-3-{N-(3-phenylpropionoyl)- β -(2-naphthyl)-L-alanyl}-amino-4-phenylthio-azetidin-2-one;
20 (3S,4SR)-3-{N-(3-phenylpropionoyl)- β -(2-naphthyl)-L-alanyl}-amino-4-phenylsulphonyl-azetidin-2-one;
(3S,4SR)-3-{N-(3-phenylpropionoyl)- β -(2-naphthyl)-L-alanyl}-amino-4-(2-hydroxy ethyl thio)-azetidin-2-one;
(3S,4SR)-3-{N-(3-phenylpropionoyl)- β -(2-naphthyl)-L-alanyl}-amino-4-
25 benzyloxy-azetidin-2-one;
(3S,4SR)-3-{N-(3-phenylpropionoyl)- β -(2-naphthyl)-L-alanyl}-amino-4-cyclohexyloxy-azetidin-2-one;
(3S,4S)-3-{N-(trans-2-phenyl-eth-1-enesulfonyl)- β -(2-naphthyl)-L-alanyl}-amino-4-acetoxy-azetidin-2-one;
30 (3S,4SR)-3-{N-(3-phenylpropionoyl)- β -(2-naphthyl)-L-alanyl}-amino-4-{4-(2S-2-amino-2-carboxyethyl)-phenoxy}-azetidin-2-one;
(3S,4S)-3-{N-(benzylaminocarbonyl)- β -(2-naphthyl)-L-alanyl}-amino-4-

acetoxy-azetidin-2-one;

(3S,4SR)-3-{N-(benzylaminocarbonyl)- β -(2-naphthyl)-L-alanyl}-
amino-4-{4-(2S-2-amino-2-carboxyethyl)-phenoxy}-azetidin-2-one;

(3S,4S)-3-{N-(3-phenylpropionoyl)-L-citrullinyl}-amino-4-
5 acetoxy-azetidin-2-one; and

(3S,4S)-3-{N-(2-phenyl-eth-1-en-sulphonyl)- β -(2-naphthyl)-L-alanyl}-
amino-4-acetoxy-azetidin-2-one;

(3S,4S)-3-{N ^{α} -(3-phenylpropionyl)-N ^{ϵ} -nitro-L-arginyl}-
amino-4-acetoxy-azetidin-2-one;

10 (3S,4R)-3-(2S-2-benzyloxycarbonylamino-2-t-butyloxymethyl -
acetamido)-4-phenoxy-azetidin-2-one;

(3S,4R)-3-[2S-2-benzyloxycarbonylamino-2-(1-t-butyloxyethyl) -
acetamido]-4-phenoxy-azetidin-2-one;

(3S, 4S)-3-(2S-2-benzyloxycarbonylamino-2-t-butylmethyl-acetamido)-
15 4-phenoxy-azetidin-2-one;

(3S,4S)-3-[2S-2-(3-phenylpropionoyl)amino-2-t-butylmethyl-acetamido]-
4-phenoxy-azetidin-2-one;

(3S,4S)-3-[2S-2-(3-phenylpropionoyl)amino-2-t-butyl-acetamido]-4-
phenoxy-azetidin-2-one;

20 (3S,4S)-3-[2S-2-(3-phenylpropionoyl) amino-2-(3, 4-dimethoxyphenyl)
methyl- acetamido]-4-phenoxy-azetidin-2-one;

(3S,4S)-3-[2S-3-phenylpropionoyl) amino-2-(3,4-
ethylenedioxyphenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one;

(3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(3-benzothienylmethyl)-
25 acetamido]-4-phenoxy-azetidin-2-one;

(3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(4,4'-biphenylmethyl)-
acetamido]-4-phenoxy-azetidin-2-one;

(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(2-chloro-phenylmethyl)-
acetamido]-4-phenoxy-azetidin-2-one;

30 (3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(4-chloro-phenylmethyl)-
acetamido]-4-phenoxy-azetidin-2-one;

(3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(3,4-dichloro -

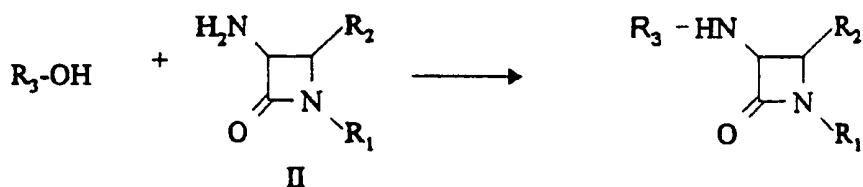
- phenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one;
 (3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(diphenylmethyl) -
 acetamido]-4-phenoxy-azetidin-2-one;
 (3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(2-fluoro-phenylmethyl)-
 5 acetamido]-4-phenoxy-azetidin-2-one;
 (3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(4-fluoro-phenylmethyl)-
 acetamido]-4-phenoxy-azetidin-2-one;
 (3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(3,4-difluoro -
 phenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one;
 10 (3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(4-iodo-phenylmethyl)-
 acetamido]-4-phenoxy-azetidin-2-one;
 (3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(naphth-1-yl)methyl -
 acetamido]-4-phenoxy-azetidin-2-one;
 (3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(4-nitro-phenylmethyl)-
 15 acetamido]-4-phenoxy-azetidin-2-one;
 (3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(pentafluorophenyl -
 methyl)-acetamido]-4-phenoxy-azetidin-2-one;
 (3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(4-thiazolylmethyl)-
 acetamido]-4-phenoxy-azetidin-2-one;
 20 (3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(3-trifluoromethylphenyl-
 methyl)-acetamido]-4-phenoxy-azetidin-2-one;
 (3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(3-sulfamoylmethyl) -
 acetamido]-4-phenoxy-azetidin-2-one;
 (3S,4S)-3-[2S-2-(3-phenylpropionoyl) amino-2-(3,4-
 25 methylenedioxyphenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one;
 (3S,4S)-3-[2S-2-(3-phenylpropionoyl) amino-2-(3,4-
 diisopropoxyphenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one;
 (3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-butyl-acetamido]-4-
 phenoxy-azetidin-2-one; and
 30 (3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-propyl-acetamido]-4 -
 phenoxy-azetidin-2-one.

Compounds of formula I may be utilized for different diseases such as

muscular dystrophy, myocardial infarction, bone resorption, arthritis, cancer metastasis, pulmonary emphysema, septic shock, cerebral ischemia, memory function, Alzheimer and cataract, malaria, glomerular basement membrane degradation, bacterial infection, inflammatory diseases, parasitic infections, and viral infections by inhibiting the cysteine proteinase in medicaments formulated with pharmaceutically acceptable carriers.

Description of Preferred Embodiments

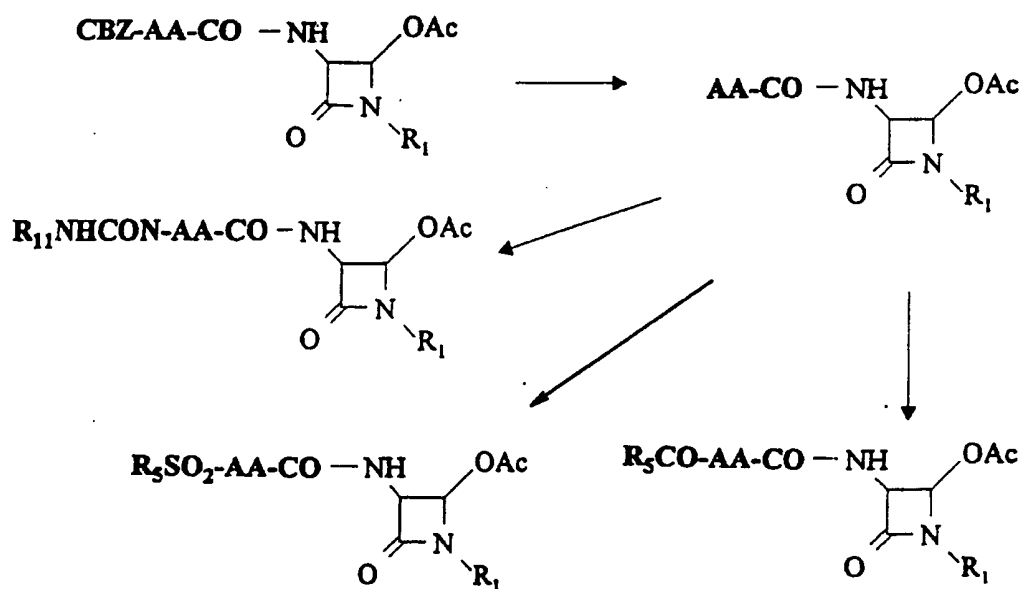
The present invention relates to the certain 3,4-disubstituted-azetidin-2-one derivatives having excellent cysteine proteinase inhibitory activity and selectivity among cysteine proteinase enzymes. The compounds of this invention are characterized by having hydrogen, ester (OCOR₅), ether (OR₅), thioether (SR₅), SOR₅, SO₂R₅ at position 4 of azetidin-2-one. Certain derivatives of formula I were prepared by the common intermediates II by reacting with substituted unnatural amino acids either in presence of dicyclohexylcarbodiimide (DCC) or acid chloride in presence of base, or activated ester according to techniques known in the art.



The preparation of compounds II were carried out by following the synthetic route as described in Eur. J. Med. Chem 1992, 27, 131-140, and Tetrahedron 1983, 39, 2577-2589, wherein R₂ is OCOR₅, and R₃ is an amino acid residue with a COOR₈ substituent. The definitions of R₁, R₅ and R₈ are the same as defined above.

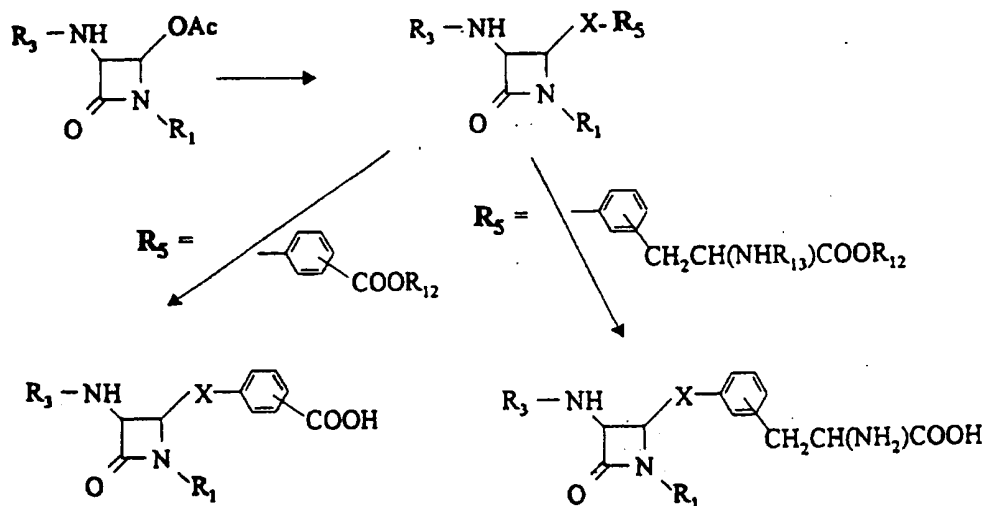
Certain 3,4-disubstituted-azetidin-2-one derivatives of formula I wherein substitutions at amino acid group are other than COOR₅, such as

COR₅ or SO₂R₅, were prepared by following the synthetic route as shown in the scheme depicted below, wherein "AA" refers to an α-amino acid residue as disclosed herein. The R₅ groups are the same as defined above. The benzyloxycarbonyl substituted unnatural amino acid were desubstituted and resubstituted through amide bond by reacting with R₅-COOH either in presence of DCC or acid chloride in presence of base or anhydride in presence of base or activated ester, or through sulphonamide bond by reacting with R₅SO₂Cl in presence of base or through urea bond by reacting with R₁₁NCO. R₁₁ is a C₁-C₈ alkyl group which may be substituted with phenyl or heterocyclic group.



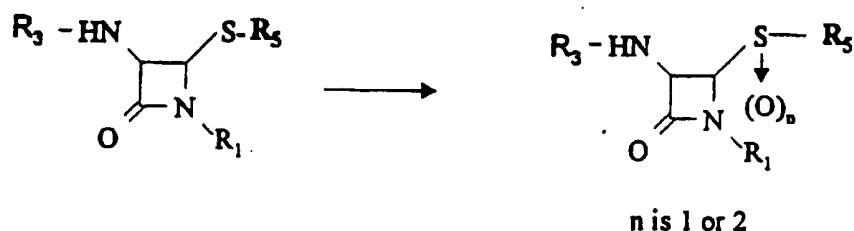
Certain 3,4-disubstituted-azetidin-2-one derivatives of formula I wherein R₂ is XR₅, wherein X is O or S, and R₆ is the same as defined above, were

prepared by following the synthetic route as shown below starting from compound of formula I wherein R_2 is OCOCH_3 by reacting with $R_5\text{XH}$ in presence of lewis acids such as zinc acetate, zinc iodide, zinc chloride, titanium tetrachloride, palladium acetate, boron trifluoride, aluminium trichloride and the like or in presence of base such as sodium hydroxide. In certain cases where carboxy group as substituent in R_5 is substituted with R_{12} such as diphenyl methyl or 1,1-dimethyl ethyl, or amino group as substituent in R_5 is substituted with R_{13} such as benzyloxy carbonyl or 1,1-dimethyl ethoxy carbonyl, or both groups as substituents in R_5 together were desubstituted by hydrogenation or hydrolysis with acids.

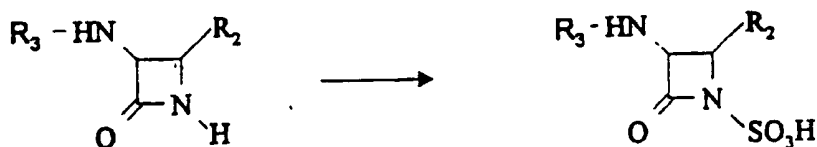


Certain 3,4-disubstituted-azetidin-2-one derivatives of formula I wherein R_2 is SR_5 were converted to SOR_5 or SO_2R_5 by oxidation with oxidizing agent selected from m-chloroperbenzoic acid, hydrogen peroxide, peracetic acid, potassium permanganate, manganese dioxide and the like. The

synthetic route is outlined below.



3,4-Disubstituted-azetidin-2-one derivatives of formula I wherein R_1 is hydrogen can be converted to N-sulphonic acid by the sulphonation with pyridine- SO_3 or dimethylformamide- SO_3 complex by following the synthetic route as outlined below.



In the above descriptions, the reactants are reacted together with solvent at elevated or low temperatures for sufficient time to allow the reaction to proceed to completion. The reaction conditions will depend upon the nature and reactivity of the reactants. Wherever a base is used in a reaction, they are selected from triethylamine, pyridine, 4-dimethylaminopyridine, diisopropylethylamine, 1,5-diazabicyclo[4,3,0]non-5-ene, 1,8-diazabicyclo[5,4,0]undec-7-ene, sodium carbonate, potassium carbonate or cesium carbonate.

The solvent of choice for the reaction are selected from non reactive solvents depending on the reactants such as benzene, toluene, acetonitrile, tetrahydrofuran, ethanol, methanol, chloroform, ethyl acetate, methylene

chloride, dimethyl formamide, dimethyl sulfoxide, hexamethyl phosphoric triamide, or the like. Solvent mixtures may also be utilized.

Reaction temperatures would generally be in the range of from -70°C to 150°C. The preferred molar ratio of reactants are 1:1 to 5.0. The reaction
5 time is in the range of from 0.5 to 72 hours, depending on the reactants.

The desubstitution of N-substituted group is carried out either by hydrogenation or by hydrolysis with appropriate acids such as hydrochloric acid, trifluoroacetic acid or acetic acid in solvent such as methanol, ethanol, propanol or ethyl acetate. The hydrogenation reaction is usually carried out
10 in the presence of a metal catalyst, such as Pd, Pt, or Rh, under normal pressure to high pressure.

The compounds of this invention, when used alone or in combination with other drugs as an agent for treating muscular dystrophy, myocardial infarction, bone resorption, arthritis, cancer metastasis, pulmonary
15 emphysema, septic shock, cerebral ischemia, memory function, Alzheimer and cataract, malaria, glomerular basement membrane degradation, bacterial infection, inflammatory diseases, parasitic infections, and viral infections, in mammals including humans, may take pharmaceutical dosage forms including parenteral preparations such as injections, suppositories, aerosols and the
20 like, and oral preparations such as tablets, coated tablets, powders, granules, capsules, liquids and the like. Injections are generally preferred. The above preparations are formulated in a manner known in the art.

For the formulation of solid preparations for oral administration, an excipient, and if desired, a binder, disintegrator, lubricant, coloring agent,
25 corrigent, flavor etc. are added to the compound of the invention, and then tablets, coated tablets, granules, powders, capsules or the like are prepared in a conventional manner.

For the formulation of injections, a pH adjusting agent, buffer, stabilizer, isotonic agent, local anesthetic or the like is added to the active ingredient of
30 the invention, and injections for subcutaneous, intramuscular or intravenous administration can be prepared in the conventional manner.

For the formulation of suppositories, a base, and if desired, a surfactant

are added to the active ingredient of the invention, and the suppositories are prepared in a conventional manner.

The excipients useful for solid preparations for oral administration are those generally used in the art, and the useful examples are excipients such as lactose, sucrose, sodium chloride, starches, calcium carbonate, kaolin, crystalline cellulose, methyl cellulose, glycerin, sodium alginate, gum arabic and the like, binders such as polyvinyl alcohol, polyvinyl ether, polyvinyl pyrrolidone, ethyl cellulose, gum arabic, schellac, sucrose, water, ethanol, propanol, carboxymethyl cellulose, potassium phosphate and the like, lubricants such as magnesium stearate, talc and the like, and further include additives such as usual known coloring agents, disintegrators and the like. Examples of bases useful for the formulation of suppositories are oleaginous bases such as cacao butter, polyethylene glycol, lanolin, fatty acid triglycerides, witpsol (trademark, Dynamite Nobel Co. Ltd.) and the like. Liquid preparations may be in the form of aqueous or oleaginous suspension, solution, syrup, elixir and the like, which can be prepared by a conventional way using additives.

The amount of the compound I of the invention to be incorporated into the pharmaceutical composition of the invention varies with the dosage form, solubility and chemical properties of the compound, administration route, administration scheme and the like. Preferably the amount is about 1 to 25 w/w% in the case of oral preparations, and about 0.1 to about 5 w/w% in the case of injections which are parenteral preparations.

The dosage of the compound I of the invention is suitably determined depending on the individual cases taking symptoms, age and sex of the subject and the like into consideration. Usually the dosage in the case of oral administration is about 50 to 1500 mg per day for an adult in 2 to 4 divided doses, and the dosage in the case of injection, for example, by intravenous administration is 2 ml (about 1 to 100 mg) which is administered once a day for adults wherein the injection may be diluted with physiological saline or glucose injection liquid if so desired, and slowly administered over at least 5 minutes. The dosage in case of suppositories is about 1 to 1000 mg which is

administered once or twice a day at an interval of 6 to 12 hours wherein the suppositories are administered by insertion into the rectum.

Example 1

5 (3S,4S)-3-(1-N-benzyloxycarbonyl-2-indolinecarbonyl)-amino-4-acetoxy-azetidin-2-one (1)

(3S,4S)-3-benzyloxycarbonylamino-4-acetoxy-azetidin-2-one (278 mg, 1 mmol) was hydrogenated with 300 mg of 10 % palladium on activated carbon in 25 ml of ethyl acetate at 50 psi hydrogen pressure at room temperature for 1.5 hrs. After removal of catalyst by filtration, desubstituted
10 (3S,4S)-3-amino-4-acetoxy-azetidin-2-one in ethyl acetate was obtained.

To a solution of 1-benzyloxycarbonyl-2-indoline carboxylic acid (320 mg, 1.05 mmol) and triethylamine (106 mg, 1.05 mmol) in chloroform (20 ml), ethyl chloroformate (109 mg, 1 mmol) was added at -15 °C. The reaction mixture was stirred at a bath temperature of -10 to 5 °C for 1 hr. Then a
15 precooled solution of (3S,4S)-3-amino-4-acetoxy-azetidin-2-one in ethyl acetate was added at -15 °C and stirring was continued at a bath temperature of -15 to 5 °C for 1 hr. After removal of solvent, the residue was dissolved in ethyl acetate, washed with water, brine and dried over sodium sulfate. After
20 removal of solvent, the residue was purified by silica gel column chromatography using hexane-ethyl acetate (1:3) as eluent and the title compound was obtained.

Yield: 71 %.

m.p.: 196-197 °C

FAB-MS: 424 (MH⁺), calcd for C₂₂H₂₁N₃O₆ 423

25 ¹H NMR (DMSO-d₆), δ (ppm): 2.05 (3H, s), 2.90-3.05 (1H, m), 3.45-3.65 (1H, m), 4.65 (1H, m), 4.90 (1H, m), 5.17 (2H, s), 5.70 (1H, s), 6.95-7.40 (9H, m), 8.95 (1H, d, J=8Hz), 9.20 (1H, s).

IR (KBr, cm⁻¹): 3300, 1800, 1745, 1716, 1670, 1541, 1485, 1408, 1363, 1275, 1223.

Example 2

(3S,4S)-3-(N-benzyloxycarbonyl-D-phenylglycyl)-amino-4-acetoxy-

azetidin-2-one (2)

To a solution of N-benzyloxycarbonyl-D-phenylglycine (285 mg, 1.0 mmol) and 1-hydroxybenzotriazole (135 mg, 1.0 mmol) in THF (20 ml), DCC (206 mg, 1.0 mmol)/THF (10 ml) was added at 0 °C. The reaction mixture was stirred at room temperature for 2 hrs and then cooled with an ice bath. The resulting DCU was removed by filtration. Then a precooled solution of (3S,4S)-3-amino-4-acetoxy-azetidin-2-one in ethyl acetate was added at -15 °C and the resulting mixture was stirred at a bath temperature of -15 to 5 °C for 1 hr and then at room temperature for 4 hrs. After removal of solvent, the residue was dissolved in ethyl acetate, washed with cold saturated NaHCO₃ solution, water, brine and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography using hexane-ethyl acetate (1:2) as eluent and the title compound was obtained.

Yield: 71 %.

m.p.: 181-182 °C

FAB-MS: 412 (MH⁺), calcd for C₂₁H₂₁N₃O₆ 411

¹H NMR (DMSO-d₆), δ (ppm): 2.07 (3H, s), 4.61 (1H, d, J=8 Hz), 5.05 (2H, s), 5.25 (1H, d, J=8.3 Hz), 5.71 (1H, s), 7.25-7.45 (10H, m), 8.06 (1H, d, J=8.3 Hz), 8.99 (1H, d, J=8 Hz), 9.20 (1H, s).

IR (KBr, cm⁻¹): 3375, 1796, 1749, 1721, 1690, 1663, 1530, 1505, 1373, 1328, 1250, 1228.

Example 3(3S,4S)-3-(N-benzyloxycarbonyl-DL-phenylglycyl)-amino-4-acetoxy-azetidin-2-one (3)

By a similar method as described in example 2, the title compound was obtained by reacting N-benzyloxycarbonyl-DL-phenylglycine with (3S,4S)-3-amino-4-acetoxy-azetidin-2-one.

Yield: 50 %.

m.p.: 145-146 °C

FAB-MS: 412 (MH⁺), calcd for C₂₁H₂₁N₃O₆ 411

¹H NMR (DMSO-d₆), δ (ppm): 2.07 (3H, s), 4.66 (1H, d, J=8.4 Hz), 5.05 (2H, s), 5.25 (1H, d, J=8.4 Hz), 5.71 (1H, s), 7.25-7.45 (10H, m), 8.06 (1H, d,

J=8.4 Hz), 8.97 (1H, m), 9.21 (1H, s).

IR (KBr, cm^{-1}): 3375, 1799, 1743, 1688, 1660, 1533, 1372, 1324, 1250, 1226.

Example 4

5 (3S,4S)-3-(N-benzyloxycarbonyl-L-homophenylalanyl)-amino-4 -
acetoxy-azetidin-2-one (4)

By a similar method as described in example 1, the title compound was obtained by reacting N-benzyloxycarbonyl-L-homophenylalanine with (3S,4S)-3-amino-4-acetoxy-azetidin-2-one.

10 Yield: 45 %.

m.p.: 180-181 °C

FAB-MS: 440 (MH^+), calcd for $\text{C}_{23}\text{H}_{25}\text{N}_3\text{O}_6$ 439

^1H NMR (DMSO-d_6), δ (ppm): 1.75-1.95 (2H, m), 2.08 (3H, s), 2.60 (2H, m), 4.04 (1H, m), 4.65 (1H, d, J=8 Hz), 5.06 (2H, m), 5.76 (1H, s), 7.15-7.40
15 (10H, m), 7.65 (1H, d, J=8 Hz), 8.70 (1H, d, J=8 Hz), 9.18 (1H, s).

IR (KBr, cm^{-1}): 3310, 1802, 1748, 1687, 1660, 1555, 1532, 1367, 1242.

Example 5

(3S,4S)-3-(N-benzyloxycarbonyl- β -(3-pyridyl)-L-alanyl)-amino-4 -
acetoxy-azetidin-2-one (5)

20 By a similar method as described in example 2, the title compound was obtained by reacting N-benzyloxycarbonyl- β -(3-pyridyl)-L-alanine with (3S,4S)-3-amino-4-acetoxy-azetidin-2-one.

Yield: 75 %.

m.p.: 186 °C (dec.)

25 FAB-MS: 427 (MH^+), calcd for $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_6$ 426

^1H NMR (DMSO-d_6), δ (ppm): 2.09 (3H, s), 2.75-3.15 (2H, m), 4.28 (1H, m), 4.66 (1H, d, J=8.3 Hz), 4.94 (2H, m), 5.75 (1H, s), 7.15-7.40 (6H, m), 7.65-7.75 (2H, m), 8.40-8.55 (2H, m), 8.85 (1H, d, J=8 Hz), 9.21 (1H, s).

IR (KBr, cm^{-1}): 3300, 1792, 1743, 1690, 1662, 1534, 1373, 1227.

30

Example 6

(3S,4S)-3-(N-benzyloxycarbonyl- β -(2-pyridyl)-L-alanyl)-amino-4 -

acetoxy-azetidin-2-one (6)

By a similar method as described in example 2, the title compound was obtained by reacting N-benzyloxycarbonyl- β -(2-pyridyl)-L-alanine with (3S,4S)-3-amino-4-acetoxy-azetidin-2-one.

5 Yield: 19 %.

m.p.: 115-117 °C

FAB-MS: 427 (MH⁺), calcd for C₂₁H₂₂N₄O₆ 426

¹H NMR (CDCl₃), δ (ppm): 2.10 (3H, s), 3.28 (2H, m), 4.70 (2H, m), 5.08 (2H, s), 5.72 (1H, s), 6.63 (1H, m), 7.10-7.40 (8H, m), 7.55-7.65 (1H, m),
10 8.35-8.50 (2H, m).

IR (KBr, cm⁻¹): 3315, 1792, 1741, 1716, 1686, 1655, 1526, 1256, 1222.

Example 7(3S,4S)-3-(N-benzyloxycarbonyl- β -(2-thienyl)-DL-alanyl)-amino-4-acetoxy-azetidin-2-one (7)

15 By a similar method as described in example 2, the title compound was obtained by reacting N-benzyloxycarbonyl- β -(2-thienyl)-DL-alanine with (3S,4S)-3-amino-4-acetoxy-azetidin-2-one.

Yield: 61 %.

m.p.: 68-69 °C

20 FAB-MS: 432 (MH⁺), calcd for C₂₀H₂₁N₃O₆S 431

¹H NMR (DMSO-d₆), δ (ppm): 2.09 (3H, s), 2.95-3.30 (2H, m), 4.21 (1H, m), 4.64 (0.5H, d, J=8 Hz), 4.68 (0.5H, d, J=8 Hz), 5.00 (2H, m), 5.68 (0.5H, s), 5.75 (0.5H, s), 6.85-6.95 (2H, m), 7.25-7.40 (6H, m), 7.68 (0.5H, d, J=8 Hz), 7.72 (0.5H, d, J=8 Hz), 8.86 (0.5H, d, J=8 Hz), 8.88 (0.5H, d, J=8 Hz), 9.21
25 (0.5H, s), 9.22 (0.5H, s).

IR (KBr, cm⁻¹): 3300, 1790, 1747, 1718, 1697, 1670, 1536, 1506, 1225.

Example 8(3S,4S)-3-(N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl)-amino-4-acetoxy-azetidin-2-one (8)

30 By a similar method as described in example 2, the title compound was obtained by reacting N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanine with (3S,4S)-3-amino-4-acetoxy-azetidin-2-one.

Yield: 61 %.

m.p.: 172-173 °C

FAB-MS: 476 (MH⁺), calcd for C₂₆H₂₅N₃O₆ 475

¹H NMR (DMSO-d₆), δ (ppm): 2.07 (3H, s), 2.85-3.25 (2H, m), 4.38 (1H, m),
5 4.63 (1H, d, J=8 Hz), 4.92 (2H, m), 5.76 (1H, s), 7.05-7.25 (5H, m), 7.40-
7.55 (3H, m), 7.67 (1H, d, J=8.7 Hz), 7.75-7.95 (4H, m), 8.85 (1H, d, J=8
Hz), 9.21 (1H, s).

IR (KBr, cm⁻¹): 3370, 1800, 1773, 1688, 1661, 1527, 1262, 1218.

Example 9

10 (3S,4S)-3-(N-benzyloxycarbonyl-β-(3-fluorophenyl)-L-alanyl)-amino-4-
acetoxy-azetidin-2-one (9)

By a similar method as described in example 1, the title compound was
obtained by reacting N-benzyloxycarbonyl-β-(3-fluorophenyl)-L-alanine with
(3S,4S)-3-amino-4-acetoxy-azetidin-2-one.

15 Yield: 52 %.

m.p.: 166-167 °C

FAB-MS: 444 (MH⁺), calcd for C₂₂H₂₂FN₃O₆ 443

¹H NMR (DMSO-d₆), δ (ppm): 2.11 (3H, s), 2.75-3.15 (2H, m), 4.28 (1H, m),
4.67 (1H, d, J=8 Hz), 4.97 (2H, m), 5.78 (1H, s), 7.00-7.40 (9H, m), 7.65
20 (1H, d, J=8.7 Hz), 8.84 (1H, d, J=8 Hz), 9.22 (1H, s).

IR (KBr, cm⁻¹): 3310, 1789, 1747, 1698, 1668, 1528, 1371, 1250, 1225.

Example 10

(3S,4S)-3-(N-benzyloxycarbonyl-β-(4-methoxyphenyl)-L-alanyl)-amino-
4-acetoxy-azetidin-2-one (10)

25 By a similar method as described in example 1, the title compound was
obtained by reacting N-benzyloxycarbonyl-β-(4-methoxyphenyl)-L-alanine with
(3S,4S)-3-amino-4-acetoxy-azetidin-2-one.

Yield: 28 %.

m.p.: 112-113 °C

30 FAB-MS: 456 (MH⁺), calcd for C₂₃H₂₅N₃O₆ 455

¹H NMR (CdCl₃), δ (ppm): 2.11 (3H, s), 3.02 (2H, d, J=6.4 Hz), 3.77 (3H, s),
4.42 (1H, m), 4.59 (1H, d, J=7.3 Hz), 5.06 (2H, s), 5.38 (1H, d, J=7 Hz),

5.77 (1H, s), 6.80 (4H, m), 7.09 (2H, d, J=8.5 Hz), 7.25-7.40 (5H, m).
IR (KBr, cm⁻¹): 3380, 1811, 1748, 1680, 1524, 1369, 1286, 1245.

Example 11

5 (3S,4S)-3-{N-benzyloxycarbonyl-β-(2-naphthyl)-L-alanyl}-amino-4-phenoxy-azetidin-2-one (11)

To a solution of phenol (30 mg, 0.32 mmol) in acetone (2 ml) and 1 N NaOH (0.25 ml), (3S,4S)-3-{N-benzyloxycarbonyl-β-(2-naphthyl)-L-alanyl}-amino-4-acetoxy-azetidin-2-one (95 mg, 0.2 mmol) in acetone (1 ml) and THF (2 ml) was added at 5 °C. The mixture was stirred at 5 °C for 1 hr and then
10 at room temperature for 1 hr. After removal of solvent, the residue was dissolved in ethyl acetate, washed with water, brine and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography using ethyl acetate-hexane (1:2) as eluent and 45 mg of (3S,4S)-3-{N-benzyloxycarbonyl-β-(2-naphthyl)-L-alanyl}-amino-4-phenoxy-
15 azetidin-2-one was obtained.

Yield: 44%.

m.p.: 205-206 °C

FAB-MS: 510 (MH⁺), calcd for C₃₀H₂₇N₃O₅ 509

¹H NMR (DMSO-d₆), δ (ppm): 2.85-3.30 (2H, m), 4.38 (1H, m), 4.70 (1H, d, J=8.2 Hz), 4.94 (2H, m), 5.55 (1H, s), 6.85-7.90 (18H, m), 8.99 (1H, d, J=8.3 Hz), 9.34 (1H, s).
20

IR (KBr, cm⁻¹): 3280, 1798, 1681, 1654, 1525, 1489, 1351, 1298, 1229.

Example 12

25 (3S,4S)-3-{N-benzyloxycarbonyl-β-(2-naphthyl)-L-alanyl}-amino-4-(3-methyl phenoxy)-azetidin-2-one (12A) and (3S,4R)-3-{N-benzyloxycarbonyl-β-(2-naphthyl)-L-alanyl}-amino-4-(3-methylphenoxy)-azetidin-2-one (12B)

By a similar method as described in example 11, the title compounds (12A) and (12B) were obtained by reacting (3S,4S)-3-{N-benzyloxycarbonyl-β-(2-naphthyl)-L-alanyl}-amino-4-acetoxy-azetidin-2-one with 3-methylphenol.

30 For (12A):

Yield: 29 %.

m.p.: 108.5 -109.5 °C.

FAB-MS: 524 (MH^+), calcd for $C_{31}H_{29}N_3O_5$ 523

1H NMR ($DMSO-d_6$), δ (ppm): 2.27 (3H, s), 2.90-3.30 (2H, m), 4.35-4.45 (1H, m), 4.67 (1H, d, $J=8.3$ Hz), 4.92 (2H, m), 5.53 (1H, s), 6.69 (2H, m), 6.84 (1H, d, $J=7.4$ Hz), 7.10-7.25 (6H, m), 7.40-7.50 (3H, m), 7.70-7.90 (5H, m), 8.97 (1, d, $J=8.3$ Hz), 9.32 (1H, s).

IR (KBr, cm^{-1}): 3265, 1793, 1682, 1652, 1588, 1526, 1354, 1278, 1249.

For (12B):

Yield: 16 %.

m.p.: 216 -218 °C.

10 FAB-MS: 524 (MH^+), calcd for $C_{31}H_{29}N_3O_5$ 523

1H NMR ($DMSO-d_6$), δ (ppm): 2.25 (3H, s), 2.75-3.20 (2H, m), 4.40-4.50 (1H, m), 4.86 (2H, s), 5.42 (1H, m), 5.73 (1H, d, $J=3.8$ Hz), 6.70-6.85 (3H, m), 7.10-7.25 (6H, m), 7.40-7.60 (4H, m), 7.75-7.90 (4H, m), 8.95 (1H, d, $J=9.2$ Hz), 9.31 (1H, s).

15 IR (KBr, cm^{-1}): 3285, 1780, 1663, 1588, 1537, 1251.

Example 13

(3S,4S)-3-(N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl)-amino-4-(2-naphthoxy)-azetidin-2-one (13A) and (3S,4R)-3-(N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl)-amino-4-(2-naphthoxy)-azetidin-2-one (13B)

20 By a similar method as described in example 11, the title compounds (13A) and (13B) were obtained by reacting (3S,4S)-3-(N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl)-amino-4-acetoxy-azetidin-2-one with 2-naphthol.

For (13A):

Yield: 13 %.

25 m.p.: 224 - 225 °C.

FAB-MS: 560 (MH^+), calcd for $C_{34}H_{29}N_3O_5$ 559

1H NMR ($DMSO-d_6$), δ (ppm): 3.0-3.4 (2H, m), 4.45-4.55 (1H, m), 4.77 (1H, d, $J=8.4$ Hz), 4.97 (2H, m), 5.71 (1H, s), 7.15-7.30 (7H, m), 7.40-7.60 (5H, m), 7.80-7.95 (8H, m), 9.11 (1H, d, $J=8.4$ Hz), 9.43 (1H, s).

30 IR (KBr, cm^{-1}): 3305, 1792, 1649, 1535, 1372, 1275.

For (13B):

Yield: 13 %.

m.p.: 109 - 110 °C.

FAB-MS: 560 (MH⁺), calcd for C₃₄H₂₉N₃O₅ 559

¹H NMR (DMSO-d₆), δ (ppm): 2.75-3.10 (2H, m), 4.35-4.50 (1H, m), 4.78 (2H, m), 5.45-5.55 (1H, m), 5.92 (1H, d, J=3.7 Hz), 7.05-7.60 (13H, m),

5 7.70-7.90 (7H, m), 9.02 (1H, d, J=9.0), 9.43 (1H, s).

IR (KBr, cm⁻¹): 3290, 1788, 1665, 1529, 1358, 1249.

Example 14

(3S,4S)-3-{N-benzyloxycarbonyl-β-(2-naphthyl)-L-alanyl}-amino-4-{3-(morpholin-4-yl)-phenoxy}-azetidin-2-one (14A) and (3S,4R)-3-{N-benzyloxycarbonyl-β-(2-naphthyl)-L-alanyl}-amino-4-{3-(morpholin-4-yl)-phenoxy}-azetidin-2-one (14B)

By a similar method as described in example 11, the title compounds (14A) and (14B) were obtained by reacting (3S,4S)-3-{N-benzyloxycarbonyl-β-(2-naphthyl)-L-alanyl}-amino-4-acetoxy-azetidin-2-one with 3-(morpholin-4-yl)-phenol.

For (14A):

Yield: 15 %.

m.p.: 140 °C (dec.)

FAB-MS: 595 (MH⁺), calcd for C₃₄H₃₄N₄O₆ 594

20 ¹H NMR (DMSO-d₆), δ (ppm): 2.90-3.30 (6H, m), 3.70-3.80 (4H, m), 4.35-4.50 (1H, m), 4.70 (1H, d, J=8.1 Hz), 4.95 (2H, m), 5.57 (1H, s), 6.36 (1H, m), 6.44 (1H, s), 6.67 (1H, m), 7.10-7.30 (6H, m), 7.45-7.55 (3H, m), 7.71 (1H, d, J=8.6 Hz), 7.80-7.95 (4H, m), 9.00 (1H, d, J=8.1 Hz), 9.35 (1H, s).

IR (KBr, cm⁻¹): 3265, 1791, 1653, 1601, 1528, 1490, 1250.

25 For (14B):

Yield: 24 %.

m.p.: 147 °C (dec.)

FAB-MS: 595 (MH⁺), calcd for C₃₄H₃₄N₄O₆ 594

30 ¹H NMR (DMSO-d₆), δ (ppm): 2.80-3.00 (1H, m), 3.07 (5H, m), 3.68 (4H, m), 4.40-4.60 (1H, m), 4.85 (2H, s), 5.40-5.50 (1H, m), 5.73 (1H, d, J=3.7 Hz), 6.40-6.55 (2H, m), 6.60-6.70 (1H, m), 7.10-7.30 (6H, m), 7.45-7.60 (4H, m), 7.80-7.95 (4H, m), 8.95 (1H, d, J=9.4), 9.31 (1H, s).

IR (KBr, cm^{-1}): 3285, 1780, 1682, 1661, 1593, 1532, 1487 1249.

Example 15

(3S,4SR)-3-{N-(3-phenylpropionoyl)- β -(2-naphthyl)-L-alanyl}-amino-4-phenylthio-azetidin-2-one (15)

5 By a similar method as described in example 11, the title compound 15 was obtained by reacting (3S,4S)-3-{N-(3-phenylpropionoyl)- β -(2-naphthyl)-L-alanyl}-amino-4-acetoxy-azetidin-2-one with thiophenol.

Yield: 67 %.

m.p.: 189 - 191 °C.

10 FAB-MS: 524 (MH^+), calcd for $\text{C}_{31}\text{H}_{29}\text{N}_3\text{O}_3\text{S}$ 523

^1H NMR ($\text{DMSO}-d_6$), δ (ppm): 2.25-2.40 (2H, m), 2.55-2.70 (2H, m), 2.85-3.00 (1H, m), 3.10-3.25 (1H, m), 4.56 (0.5H, m), 4.60-4.70 (0.5H, m), 4.70-4.90 (0.5H, m), 4.92 (0.5H, d, $J=2.3$), 5.28 (0.5H, d, $J=4.6$ Hz), 5.35-5.45 (0.5H, m), 6.95-7.20 (5H, m), 7.25-7.50 (8H, m), 7.65-7.90 (4H, m), 8.19 (1H, m), 8.84 (0.5H, d, $J=8.3$ Hz), 9.02 (0.5H, s), 9.05 (0.5H, s), 9.06 (0.5H, d, $J=8$ Hz).

15 IR (KBr, cm^{-1}): 3265, 3035, 1784, 1634, 1524, 1437, 1350, 1259, 1224.

Example 16

(3S,4SR)-3-{N-(3-phenylpropionoyl)- β -(2-naphthyl)-L-alanyl}-amino-4-phenylsulfonyl-azetidin-2-one (16)

20 A mixture of (3S,4SR)-3-{N-(3-phenylpropionoyl)- β -(2-naphthyl)-L-alanyl}-amino-4-phenylthio-azetidin-2-one (52 mg, 0.1 mmol) obtained in example 15, and KMnO_4 (24 mg, 0.15 mmol) in acetic acid (2 ml) and H_2O (0.5 ml) was stirred at 5 °C for 1 hr and then room temperature for 1 hr. One drop of H_2O_2 (30% aq) was added. The reaction mixture was partitioned between ethyl acetate and water, the organic layer was washed with water, saturated NaHCO_3 , water, brine and dried over Na_2SO_4 . After removal of the solvent, solid was washed with ether and 40 mg of the title compound was obtained.

30 Yield: 72 %.

m.p.: 175 °C (dec.)

FAB-MS: 556 (MH^+), calcd for $\text{C}_{31}\text{H}_{29}\text{N}_3\text{O}_5\text{S}$ 555

¹H NMR (DMSO-d₆), δ (ppm): 2.25-2.40 (2H, m), 2.55-2.65 (2H, m), 2.80-3.00 (1H, m), 3.05-3.25 (1H, m), 4.55-4.70 (0.5H, m), 4.80-4.95 (1.5H, m), 5.26 (0.5H, d, J=4.6 Hz), 5.50-5.60 (0.5H, m), 7.00-7.20 (5H, m), 7.30-7.95 (12H, m), 8.17 (0.5H, d, J=8 Hz), 8.22 (0.5H, d, J=8 Hz), 8.93 (1H, d, J=8.8 Hz), 9.36 (0.5H, s), 9.47 (0.5H, s).
IR (KBr, cm⁻¹): 3275, 1780, 1639, 1519, 1300.

Example 17

(3S,4SR)-3-{N-(3-phenylpropionoyl)-β-(2-naphthyl)-L-alanyl}-amino-4-(2-hydroxyethylthio)-azetidin-2-one (17)

By a similar method as described in example 11, the title compound 17 was obtained by reacting (3S,4S)-3-{N-(3-phenylpropionoyl)-β-(2-naphthyl)-L-alanyl}-amino-4-acetoxy-azetidin-2-one with 2-mercaptoethanol.

Yield: 26 %.

m.p.: 134 - 136 °C.

FAB-MS: 492 (MH⁺), calcd for C₂₇H₂₉N₃O₄S 491

¹H NMR (DMSO-d₆), δ (ppm): 2.30-2.40 (2H, m), 2.55-2.70 (4H, m), 2.85-3.00 (1H, m), 3.10-3.25 (1H, m), 3.45-3.60 (2H, m), 4.51 (0.6H, m), 5.70-5.80 (0.4H, m), 4.60-4.65 (1H, m), 4.70 (0.6H, d, J=2.3 Hz), 5.00 (0.4H, d, J=4.5 Hz), 7.00-7.20 (5H, m), 7.35-7.50 (3H, m), 7.70-7.90 (4H, m), 8.15-8.25 (1H, m), 8.70-8.90 (2H, m).

IR (KBr, cm⁻¹): 3270, 1757, 1636, 1527.

Example 18

(3S,4SR)-3-{N-(3-phenylpropionoyl)-β-(2-naphthyl)-L-alanyl}-amino-4-benzyloxy-azetidin-2-one (18)

A mixture of (3S,4S)-3-{N-(3-phenylpropionoyl)-β-(2-naphthyl)-L-alanyl}-amino-4-acetoxy-azetidin-2-one (236 mg, 0.5 mmol), benzyl alcohol (54 mg, 0.5 mmol), and zinc acetate dihydrate (110 mg, 0.5 mmol) in benzene (20 ml) and toluene (20 ml) was refluxed for 5 hrs using Dean-Stark water separator. After cooling, the reaction mixture was partitioned between ethyl acetate, containing a small volume of acetone, and water. The organic layer was washed with water, brine and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography using

hexane-ethyl acetate (1:1) as eluent and the title compound was obtained.

Yield: 23 %.

m.p.: 171 -172 °C.

FAB-MS: 522 (MH⁺), calcd for C₃₂H₃₁N₃O₄ 521

5 ¹H NMR (CDCl₃), δ (ppm): 2.30-2.50 (2H, m), 2.65-2.85 (2H, m), 3.00-3.35 (2H, m), 4.40-4.55 (2.5H, m), 4.70-4.85 (1H, m), 5.01 (0.5H, s), 5.12 (0.5H, d, J=4.5 Hz), 5.20-5.30 (0.5H, m), 7.00-7.80 (18H, m), 8.20-8.30 (1H, m), 8.46 (0.5H, s), 8.61 (0.5H, s).

IR (KBr, cm⁻¹): 3265, 1767, 1635, 1531.

10

Example 19

(3S,4SR)-3-{N-(3-phenylpropionoyl)-β-(2-naphthyl)-L-alanyl}-amino-4-cyclohexyloxy-azetidin-2-one (19).

By a similar method as described in example 18, the title compound 19 was obtained by reacting (3S,4S)-3-{N-(3-phenylpropionoyl)-β-(2-naphthyl)-L-alanyl}-amino-4-acetoxy-azetidin-2-one with cyclohexanol.

15

Yield: 35 %.

m.p.: 169 -171 °C.

FAB-MS: 514 (MH⁺), calcd for C₃₁H₃₅N₃O₄ 513

20 ¹H NMR (CDCl₃), δ (ppm): 1.10-2.10 (10H, m), 2.40-2.55 (2H, m), 2.80-2.95 (2H, m), 3.05-3.40 (2H, m), 3.95-4.10 (1H, m), 5.70-5.85 (1H, m), 6.31 (1H, m), 6.51 (1H, d, J=8.1 Hz), 7.10-7.90 (13H, m), 8.35 (1H, s), 8.64 (1H, s).

IR (KBr, cm⁻¹): 3275, 1780, 1639, 1519, 1300.

Example 20

25 (3S,4S)-3-{N-(trans-2-phenyl-eth-1-enesulfonyl)-β-(2-naphthyl)-L-alanyl}-amino-4-acetoxy-azetidin-2-one (20)

(3S,4S)-3-{N-benzyloxycarbonyl-β-(2-naphthyl)-L-alanyl}-amino-4-acetoxy-azetidin-2-one (237 mg, 0.5 mmol) obtained in example 8, was hydrogenated with 400 mg of 10% palladium on activated carbon in ethyl acetate (20 ml) and THF (10 ml) at 50 psi hydrogen pressure at room temperature for 2 hrs. After removal of catalyst by filtration, the desubstituted (3S,4S)-3{β-(2-naphthyl)-L-alanyl}-amino-4-acetoxy-azetidin-2-one was cooled to -15 °C. Then triethylamine (50 mg, 0.5 mmol) and trans-2-phenyl-

30

eth-1-ene sulfonyl chloride (101 mg, 0.5 mmol) were added at -15 °C. Stirring was continued at a bath temperature of -10 to 0 °C for 1 hr and 5 °C overnight. The reaction mixture was diluted with ethyl acetate, washed with cold saturated NaHCO₃ solution, water, brine and dried over sodium sulfate.

5 After removal of solvent, the residue was purified by silica gel column chromatography using hexane-ethyl acetate (1:1) as eluent and the title compound (30 mg) was obtained.

Yield: 12%.

m.p.: 176 °C (dec.).

10 FAB-MS: 508 (MH⁺), calcd for C₂₆H₂₅N₃O₆S 507

¹H NMR (DMSO-d₆), δ (ppm): 2.01 (3H, s), 2.70-3.20 (2H, m), 4.05-4.20 (1H, m), 4.57 (1H, d, J=7.8 Hz), 5.61 (1H, s), 6.50 (1H, d, J=15.5 Hz), 7.14 (1H, d, J=15.5 Hz), 7.25-7.50 (8H, m), 7.70-7.85 (4H, m), 8.05 (1H, d, J=7.8 Hz), 8.90 (1H, d, J=7.9 Hz), 9.22 (1H, s).

15 IR (KBr, cm⁻¹): 3285, 1774, 1661, 1515, 1315, 1222.

Example 21

(3S,4S)-3-[N-(benzylaminocarbonyl)-β-(2-naphthyl)-L-alanyl]-amino-4-acetoxy-azetidin-2-one (21)

20 By a similar method as described in example 2, the title compound was obtained by reacting N-(benzylaminocarbonyl)-β-(2-naphthyl)-L-alanine with (3S,4S)-3-amino-4-acetoxy-azetidin-2-one.

Yield: 70 %.

m.p.: 203 °C (dec.).

FAB-MS: 475 (MH⁺), calcd for C₂₆H₂₆N₄O₅ 474

25 ¹H NMR (DMSO-d₆), δ (ppm): 2.05 (3H, s), 2.85-3.20 (2H, m), 4.05-4.20 (2H, m), 4.50-4.65 (1H, m), 4.57 (1H, d, J= 8.0 Hz), 5.73 (1H, s), 6.22 (1H, d, J=8.5 Hz), 6.55 (1H, t, J=8.5 Hz), 7.05-7.20 (5H, m), 7.30-7.50 (3H, m), 7.65-7.90 (4H, m), 8.81 (1H, d, J=8.0 Hz), 9.17 (1H, s).

IR (KBr, cm⁻¹): 3325, 1799, 1744, 1652, 1626, 1555, 1222.

Example 22

(3S,4SR)-3-[N-(benzylaminocarbonyl)-β-(2-naphthyl)-L-alanyl]-

amino-4-{4-(2S-2-amino-2-carboxy-ethyl)-phenoxy}-azetidin-2-one (22)

To a solution of 4-(2S-2-tert-butyloxycarbonylamino-2-diphenylmethoxy carbonyl-ethyl)-phenol (0.585 g, 1.3 mmol) in acetone (6 ml), H₂O (3 ml) and 1 N NaOH (1.2ml), (3S,4S)-3-{N-(benzylaminocarbonyl)-β-(2-naphthyl)-L-alanyl}-amino-4-acetoxy-azetidin-2-one (0.5 g, 1.09 mmol) in acetone (10 ml) and H₂O (5 ml) was slowly added at 5 °C. The mixture was stirred at 5 °C for 2 hrs. After removal of solvent, the residue was dissolved in ethyl acetate, washed with water, brine and dried over sodium sulfate. After removal of solvent, the residue was recrystallized from ethyl acetate/hexane and 400 mg of (3S,4SR)-3-{N-(benzylaminocarbonyl)-β-(2-naphthyl)-L-alanyl}-amino-4-
 10 {[(2S-2-tert-butyloxycarbonylamino-2-diphenylmethoxycarbonyl-ethyl)-phenoxy]-azetidin-2-one was obtained as white solid.

200 mg of (3S,4SR)-3-{N-(benzylaminocarbonyl)-β-(2-naphthyl)-L-alanyl}-amino-4-[(2S-2-tert-butyloxycarbonylamino-2 -
 15 diphenylmethoxycarbonyl-ethyl)-phenoxy]-azetidin-2-one was added to a mixture of anisole (1 ml), TFA (2 ml) and DCM (1 ml) at -15 °C. The mixture was stirred at a bath temperature of -15 to 0 °C for 2 hrs. After removal of solvent, the resulting solid was washed with ether, ethyl acetate and acetonitril and 80 mg of the title compound was obtained as white solid.

20 Yield: 58 %.

m.p.: 180 °C (dec.).

FAB-MS: 596 (MH⁺), calcd for C₃₃H₃₃N₅O₆ 595

¹H NMR (DMSO-d₆), δ (ppm): 2.80-3.20 (4H, m), 3.65-3.80 (1H, m), 4.05-4.25 (2H, m), 4.50-4.65 (1H, m), 4.65 (0.7H, d, J=8Hz), 5.50 (0.7H, s), 5.35-
 25 5.50 (0.3H, m), 5.75 (0.3H, d, J=3Hz), 6.20-6.35 (1H, m), 6.55-6.70 (1H, m), 6.75-6.95 (2H, m), 7.05-7.25 (7H, m), 7.35-7.55 (3H, m), 7.70-7.90 (4H, m), 8.90-9.00 (1H, m), 9.33 (1H, s).

IR (KBr, cm⁻¹): 3280, 3035, 1763, 1631, 1549, 1503, 1357, 1225.

Example 23

30 (3S,4S)-3-{N-(3-phenylpropionyl)-L-citrullinyl}-amino-4-

acetoxy-azetidin-2-one (23)

By a similar method as described in example 2, the title compound was obtained by reacting N-(3-phenylpropionyl)-L-citrulline with (3S,4S)-3-amino-4-acetoxy-azetidin-2-one.

5 Yield: 35 %.

m.p.: 193 °C (dec.).

FAB-MS: 434 (MH⁺), calcd for C₂₀H₂₇N₅O₆ 433

¹H NMR (DMSO-d₆), δ (ppm): 1.20-1.70 (4H, m), 2.08 (3H, s), 2.40-2.50 (2H, m), 2.75-2.95 (4H, m), 4.20-4.35 (1H, m), 4.62 (1H, d, J=8.0 Hz), 5.37 (2H, s), 5.74 (1H, s), 5.89 (1H, m), 7.10-7.35 (5H, m), 8.08 (1H, d, J=8.0 Hz), 8.65 (1H, d, J=8.0 Hz), 9.18 (1H, s).

10 IR (KBr, cm⁻¹): 3290, 1793, 1738, 1652, 1541, 1363, 1323, 1216.

Example 24

15 (3S,4S)-3-{N^α-(3-phenylpropionyl)-N^ε-nitro-L-arginyl}-amino-4-acetoxy-azetidin-2-one (24)

By a similar method as described in example 1, the title compound was obtained by reacting N^α-(3-phenylpropionyl)-N^ε-nitro-L-arginine with (3S,4S)-3-amino-4-acetoxy-azetidin-2-one.

Yield: 12 %.

20 m.p.: 92 °C (dec.).

FAB-MS: 478 (MH⁺), calcd for C₂₀H₂₇N₄O₇ 477

¹H NMR (DMSO-d₆), δ (ppm): 1.30-1.75 (4H, m), 2.08 (3H, s), 2.40-2.50 (2H, m), 2.75-2.95 (2H, m), 3.05-3.20 (2H, m), 4.20-4.35 (1H, m), 4.62 (1H, d, J=8.2 Hz), 5.74 (1H, s), 7.15-7.35 (5H, m), 7.70-8.20 (1H, br), 8.08 (1H, d, J=8.1 Hz), 8.30-8.60 (1H, br), 8.66 (1H, d, J=8.2 Hz), 9.19 (1H, s).

25 IR (KBr, cm⁻¹): 3285, 1772, 1637, 1524, 1366, 1253.

Example 25

(3S,4R)-3-(2S-2-benzoyloxycarbonylamino-2-t-butyloxymethyl-acetamido)-4-phenoxy-azetidin-2-one (25)

30 To a solution of phenol (2.82 g 30 mmole) in THF (30ml) and 1N NaOH (26ml, 26 mmole), (3S, 4S)-3-benzoyloxycarbonylamino-4-acetoxy-azetidin-2-one (5.56 g, 20 mmole) in THF (40ml) and H₂O(20ml) is added

at 0°C. The mixture is stirred at 0°C for 1 hour and then at room temperature for 30 min. After removal of solvent, the residue is dissolved in ethyl acetate, washed with water, brine and dried over sodium sulphate.

After removal of solvent, the residue is purified by silica gel column

5 chromatography using hexane-ethyl acetate as eluent. 2.75 g of (3S, 4S)-3-benzyloxycarbonylamino-4-phenoxy-azetidin-2-one (A), 890 mg of (3S, 4R)-3-benzyloxycarbonylamino-4-phenoxy-azetidin-2-one (B) and 1.08 g of a mixture of (A) and (B) is obtained.

(3S, 4R)-3-benzyloxycarbonylamino-4-phenoxy-azetidin-2-one (1.85
10 g. 5.9 mmole) is hydrogenated with 2g of 10% palladium on activated carbon in THF (30ml) and ethyl acetate (30ml) at 50 psi hydrogen pressure at room temperature for 2 hours. After removal of catalyst by filtration, 810 mg of deprotected (3S, 4R)-3-amino-4-phenoxy-azetidin-2-one is obtained.

To a solution of 2S-2-benzyloxycarbonylamino-2-t-butyloxymethyl-
15 acetic acid (148 mg, 0.5 mmole), (3S, 4R)-3-amino-4-phenoxy-azetidin-2-one (80mg, 0.45 mmole) in DMF (3ml), BOP (221 mg, 0.5 mmole) and triethyl amine (101 mg, 1 mmole) is added. The reaction mixture is stirred at room temperature overnight and then diluted with ethyl acetate (50ml) and ether (50ml), washed with saturated NaHCO₃ solution, water, brine
20 and dried over sodium sulfate. After removal of solvent, the residue is purified by silica gel column chromatography using hexane-ethyl acetate as eluent and 70mg of the title compound is obtained.

Yield: 34%

m.p.: 135-136.5°C

25 ¹H-NMR (DMSO-d₆) , δ (ppm): 1.05 (9H, s), 3.25-3.40 (2H, m), 4.05-4.20 (1H,m), 5.01 (2H,s), 5.33 (1H,m), 5.73 (1H,d,J=3.8 Hz), 6.85-7.10 (3H,m), 7.15 (1H,d, J=8.6 Hz), 7.20-7.40 (7H,m), 8.66 (1H, d, J=9.1 Hz), 9.27 (1H, s).

Example 26

30 (3S, 4R)-3-[2S-2-benzyloxycarbonylamino-2-(1-t-butyloxyethyl)-

acetamido]-4-phenoxy-azetidin-2-one (26)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(1-t-butyl

5 Yield: 57%

m.p.: 62-64°C

¹H-NMR (DMSO-d₆), δ (ppm): 0.86 (3H, d, J=6 Hz), 0.98 (9H, s), 3.75-3.90 (1H,m), 3.95-4.10 (1H, m), 5.03 (2H,s), 5.39 (1H, m), 5.78 (1H, d, J=3.8 Hz), 6.80-7.10 (4H, m), 7.20-7.45 (7H,m), 8.53 (1H, d, J=9.4 Hz), 9.31 (1H, s).

Example 27(3S, 4S)-3-(2S-2-benzyloxycarbonylamino-2-t-butylmethyl-acetamido)-4-phenoxy-azetidin-2-one (27)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-t-butylmethyl-

15 Yield: 71%

m.p.: 157-158°C.

¹H-NMR (DMSO-d₆), δ (ppm): 0.90 (9H,s), 1.50-1.80 (2H,m), 4.00-4.13 (1H, m), 4.66 (1H, d, J=8.4 Hz), 5.07 (2H, AB system, J=8.2 and 12.6 Hz), 5.54 (1H, s), 6.85-7.35 (10H,m), 7.56 (1H, d, J=8.2 Hz), 8.80 (1H, d, J=8.5 Hz), 9.30 (1H, s).

Example 28(3S, 4S)-3-[2S-2-(3-phenylpropionoyl)amino-2-t-butylmethyl-acetamido]-4-phenoxy-azetidin-2-one (28)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-(3-phenylpropionoyl) amino-2-t-butylmethyl-

25 Yield: 68%

30 m.p.: 169-171°C.

¹H-NMR (DMSO-d₆), δ (ppm): 0.86 (9H,s), 1.40-1.69 (2H,m), 2.40-2.50 (2H, m), 2.82 (2H, t, J=6.4 and 8.6 Hz), 4.27-4.39 (1H, m), 4.63 (1H, d, J=8.3

Hz), 5.54 (1H, s), 6.88-7.37 (10H, m), 8.13 (1H, d, J=8.1 Hz), 8.73 (1H, d, J=8.4 Hz), 9.29 (1H, s).

Example 29

(3S, 4S)-3-[2S-2-(3-phenylpropionoyl)amino-2-t-butyl-acetamido]-4-phenoxy-azetidin-2-one (29)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-(3-phenylpropionoyl)amino-2-t-butyl-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

Yield: 43%

m.p.: 104-105°C

¹H-NMR (DMSO-d₆), δ (ppm): 0.89 (9H, s), 2.40-2.70 (2H, m), 2.82 (1H, t, J=8.2, 7.6 Hz), 4.22 (1H, d, J=9.1 Hz), 4.67 (1H, d, J=8.2 Hz), 5.55 (1H, s), 6.89-7.35 (10H, m), 7.91 (1H, d, J=9 Hz), 8.85 (1H, d, J=8.4 Hz), 9.30 (1H, s).

Example 30

(3S, 4S)-3-[2S-2-(3-phenylpropionoyl) amino-2-(3, 4-dimethoxyphenyl) methyl- acetamido]-4-phenoxy-azetidin-2-one (30)

A solution of L-3,4-dihydroxyphenylalanine (1.97g, 10 mmole) in 2N NaOH (10ml) is cooled in an ice-water bath. Hydrocinnamoyl chloride (1.8g, 10.6 mmole) in THF (2ml) and 1N NaOH (10ml) are added alternately at 0°C. The mixture is stirred at 0°C for 1 hour and then room temperature for 1 hour. The alkaline solution is washed two times with ether. The aqueous layer is acidified to pH 2 and then extracted 3 times with ethyl acetate. The ethyl acetate layer is washed with brine and dried over sodium sulfate. After removal of solvent, the residue is dissolved in acetone (20ml). Diazodiphenylmethane (1.63 g, 8.4 mmole) in acetone (20ml) is added at 0°C. The reaction mixture is stirred at 0°C for 2 hours and room temperature overnight. After removal of solvent, the residue is purified by silica gel column chromatography using hexane-ethyl acetate as eluent and 2.2g of N-(3-phenylpropionoyl)-L-3,4-dihydroxyphenylalanine diphenylmethyl ester was obtained.

A reaction mixture of N-(3-phenylpropionoyl)-L-3,4-

dihydroxyphenylalanine diphenylmethyl ester (248 mg, 0.5 mmole), CH_3I (213 mg, 1.5 mmole) and K_2CO_3 (172 mg, 1.25 mmole) in acetone (10ml) is stirred at room temperature overnight. After removal of solvent, the residue is dissolved in ethyl acetate, washed with water, brine and dried over sodium sulfate. After removal of solvent, the residue is purified by silica gel column chromatography using hexane-ethyl acetate as eluent and 160 mg of N-(3-phenylpropionoyl)-L-3,4-dimethoxyphenylalanine diphenylmethyl ester is obtained.

To a solution of N-(3-phenylpropionoyl)-L-3,4-dimethoxyphenylalanine diphenylmethyl ester (130mg, 0.25 mmole) and anisole (0.5 ml) in dichloromethane (3 ml), trifluoroacetic acid (6ml) is added at 0°C. The reaction mixture is stirred at 0°C for 1 hour and room temperature for 30 min. The solution is evaporated to dryness in vacuo and the residue triturated with ether. After removal of solvent, 80mg of 2S-2-(3-phenylpropionoyl) amino-2-(3,4-dimethoxyphenyl) methyl-acetic acid is obtained as white solid.

(3S, 4S)-3-benzyloxycarbonylamino-4-phenoxy-azetidin-2-one (63mg, 0.2 mmole) is hydrogenated with 100mg of 10% palladium on activated carbon in ethyl acetate (10ml) at 50 psi hydrogen pressure at room temperature for 2 hours. After removal of catalyst by filtration, deprotected (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one in ethyl acetate is obtained.

To a solution of 2S-2-(3-phenylpropionoyl) amino-2-(3,4-dimethoxyphenyl) methyl-acetic acid (70mg, 0.2 mmole) and 1-hydroxybenzotriazole (30mg, 0.22 mmole) in THF (4ml), DCC (41 mg, 0.2 mmole) is added. The reaction mixture is stirred at room temperature for 1 hour and then cooled with an ice bath. The resulting DCU is removed by filtration. Then a precooled solution of (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one in ethyl acetate is added at 0°C and the resulting mixture is stirred at 0°C for 1 hour and room temperature for 1 hour. After removal of solvent, the residue is dissolved in ethyl acetate, washed with saturated NaHCO_3 solution, water, brine and dried over sodium sulfate. After

removal of solvent, the residue is purified by recrystallization using hexane-ethyl acetate as solvent and 60mg of title compound is obtained as white solid.

Yield: 58%

5 m.p.: 183.5-185°C

¹H-NMR (DMSO-d₆), δ (ppm): 2.35-2.45 (2H, m), 2.65-3.05 (4H, m), 3.65 (3H, s), 3.70 (3H, s), 4.45-4.60 (1H, m), 4.64 (1H, d, J=8.4 Hz), 5.51 (1H, s), 6.70-6.95 (3H, m), 7.00-7.40 (10H, m), 8.19 (1H, d, J=8.1 Hz), 8.83 (1H, d, J=8.3 Hz), 9.32 (1H, s).

10

Example 31

(3S, 4S)-3-[2S-3-phenylpropionoyl] amino-2-(3,4-ethylenedioxyphenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one (31)

A reaction mixture of N-(3-phenylpropionoyl)-L-3,4-dihydroxyphenylalanine diphenylmethyl ester (360 mg, 0.72 mmole), 1-bromo-2-chloromethane (0.5 ml) and Cs₂CO₃ (472mg, 1.45 mmole) in DMF (5ml) is stirred at room temperature overnight and then at 90°C for 1 hour. The reaction mixture is diluted with ethyl acetate and ether, and washed with water, brine and dried over sodium sulfate. After removal of solvent, the residue is purified by silica gel column chromatography using hexane-ethyl acetate as eluent and 240 mg of N-(3-phenylpropionoyl)-L-(3,4-ethylenedioxyphenyl)-alanine diphenylmethyl ester is obtained.

To a solution of N-(3-phenylpropionoyl)-L-(3,4-ethylenedioxyphenyl)-alanine diphenylmethyl ester (240 mg, 0.46 mmole) and anisole (0.5 ml) in dichloromethane (3 ml), trifluoroacetic acid (6ml) is added at 0°C. The reaction mixture is stirred at 0°C for 1 hour and room temperature for 30 min. The solution is evaporated to dryness in vacuo and the residue triturated with ether. After removal of solvent, 160 mg of 2S-2-(3-phenylpropionoyl)amino-2-(3,4-ethylenedioxyphenylmethyl)-acetic acid is obtained as white solid.

30 (3S, 4S)-3-benzyloxycarbonylamino-4-phenoxy-azetidin-2-one (140 mg, 0.45 mmole) is hydrogenated with 100 mg of 10% palladium on activated carbon in ethyl acetate (20ml) at 50 psi hydrogen pressure at

room temperature for 2 hours. After removal of catalyst by filtration, deprotected (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one in ethyl acetate is obtained.

To a solution of 2S-2-(3-phenylpropionoyl) amino-2-(3,4-ethylenedioxyphenylmethyl)-acetic acid (160 mg, 0.45 mmole) and 1-hydroxybenzotriazole (66 mg, 0.49 mmole) in THF (6ml), DCC (93 mg, 0.45 mmole) is added. The reaction mixture is stirred at room temperature for 1 hour and then cooled with an ice bath. The resulting DCU is removed by filtration. Then a precooled solution of (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one in ethyl acetate is added at 0°C and the resulting mixture is stirred at 0°C for 1 hour and room temperature for 1 hour. After removal of solvent, the residue is dissolved in ethyl acetate, washed with saturated NaHCO₃ solution, water, brine and dried over sodium sulfate. After removal of solvent, the residue is purified by recrystallization using hexane-ethyl acetate as solvent and 140 mg of title compound is obtained as white solid.

Yield: 60%

m.p.: 210-212°C

¹H-NMR (DMSO-d₆) , δ (ppm): 2.35-2.45 (2H, m), 2.60-3.00 (4H,m), 4.10-4.25 (4H, s), 4.40-4.55 (1H,m), 4.62 (1H, d, J=8.4 Hz), 5.51 (1H, s), 6.65-6.95 (3H,m), 7.00-7.40 (10H, m), 8.19 (1H,d, J=8.1 Hz), 8.83 (1H, d, J=8.3 Hz), 9.32 (1H, s).

Example 32

(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(3-benzothienylmethyl)-acetamido]-4-phenoxy-azetidin-2-one (32)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(3-benzothienylmethyl)-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

Example 33

(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(4,4'-biphenylmethyl)-

acetamido]-4-phenoxy-azetidin-2-one (33)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(4,4'-biphenylmethyl)-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

Example 34(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(2-chloro-phenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one (34)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(2-chloro-phenylmethyl)-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

Example 35(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(4-chloro-phenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one (35)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(4-chloro-phenylmethyl)-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

Example 36(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(3,4-dichloro-phenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one (36)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(3,4-dichloro-phenylmethyl)-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

Example 37(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(diphenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one (37)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(diphenylmethyl)-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

Example 38(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(2-fluoro-

phenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one (38)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(2-fluoro-phenylmethyl)-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

5

Example 39

(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(4-fluoro-phenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one (39)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(4-fluoro-phenylmethyl)-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

10

Example 40

(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(3,4-difluoro-phenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one (40)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(3,4-difluoro-phenylmethyl)-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

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Example 41

(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(4-iodo-phenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one (41)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(4-iodo-phenylmethyl)-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

20

Example 42

(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(naphth-1-yl)methyl-acetamido]-4-phenoxy-azetidin-2-one (42)

25

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(naphth-1-yl)methyl-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

Example 43

(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(4-nitro-phenylmethyl)-

30

acetamido]-4-phenoxy-azetidin-2-one (43)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(4-nitro-phenylmethyl)-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

5

Example 44(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(pentafluorophenyl-methyl)-acetamido]-4-phenoxy-azetidin-2-one (44)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(pentafluorophenyl-methyl)-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

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Example 45(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(4-thiazolylmethyl)-acetamido]-4-phenoxy-azetidin-2-one (45)

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By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(4-thiazolylmethyl)-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

Example 46(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(3-trifluoromethylphenyl-methyl)-acetamido]-4-phenoxy-azetidin-2-one (46)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(3-trifluoromethylphenyl methyl)-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

25

Example 47(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(3-sulfamoylmethyl)-acetamido]-4-phenoxy-azetidin-2-one (47)

By a similar method as described in example 25, the title compound is obtained by reacting 2S-2-benzyloxycarbonylamino-2-(3-sulfamoylmethyl)-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

30

Example 48

(3S, 4S)-3-[2S-2-(3-phenylpropionoyl) amino-2-(3,4-methylenedioxyphenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one (48)

By a similar method as described in example 30, the title compound
5 is obtained by reacting 2S-2-(3-phenylpropionoyl) amino-2-(3,4-methylenedioxyphenyl)methyl acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

Example 49

(3S, 4S)-3-[2S-2-(3-phenylpropionoyl) amino-2-(3,4-diisopropoxyphenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one (49).

By a similar method as described in example 30, the title compound
is obtained by reacting 2S-2-(3-phenylpropionoyl) amino-2-(3,4-diisopropoxyphenyl)methyl acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

15 Example 50

(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-butyl-acetamido]-4-phenoxy-azetidin-2-one (50)

By a similar method as described in example 25, the title compound
is obtained by reacting 2S-2-benzyloxycarbonylamino-2-butyl-acetic acid
20 and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

Example 51

(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-propyl-acetamido]-4-phenoxy-azetidin-2-one (51)

By a similar method as described in example 25, the title compound
25 is obtained by reacting 2S-2-benzyloxycarbonylamino-2-propyl-acetic acid and (3S, 4S)-3-amino-4-phenoxy-azetidin-2-one.

Testing of inhibitors for inhibition of Cathepsin B and LTest Example 1In vitro assay procedure for cathepsin B

30 The compounds of formula I were tested for inhibition of cathepsin B using the known method (A.J. Barret et al., Biochem. J. 1982, 201, 189-198). To a 170 μ l of enzyme-buffer mixture (enzyme: r rat cathepsin B, diluted to

give approximate 10 F units/min, buffer: 56 mM sodium acetate, 1.124 mM EDTA, 10 mM DTT, pH 5.1) a 10 μ L of inhibitor (dissolved in DMSO) was added. After 10 min of incubation at room temperature, a 20 μ L of 5 mM substrate (N-CBZ-Phe-Arg-AMC, dissolved in DMSO) was added to initiate reaction. Reading is followed up for 10 min at the fluoroscan reader (excitation at 380 nm emission at 460 nm).

A plot of percentage of inhibition vs inhibitor concentration is obtained, and IC_{50} is determined using a linear regression calculation (concentration of inhibitor which will give 50% inhibition).

10

Test Example 2

In vitro assay procedure for cathepsin L

To a 170 μ L of enzyme-buffer mixture (enzyme: r rat cathepsin L, diluted to give approximate 15 F units/min, buffer: 58.8 mM sodium citrate, 1.18 mM EDTA, 235 mM sodium chloride, 5 mM DTT, pH 5.0) a 10 μ L of inhibitor (dissolved in DMSO) was added. After 10 min of incubation at room temperature, a 20 μ L of 1 mM substrate (N-CBZ-Phe-Arg-AMC, dissolved in DMSO) was added to initiate reaction. Reading is followed up for 10 min at the fluoroscan reader (excitation at 380 nm emission at 460 nm).

A plot of percentage of inhibition vs inhibitor concentration is obtained, and IC_{50} is determined using a linear regression calculation (concentration of inhibitor which will give 50% inhibition).

Table 1. In vitro inhibitory activity of monobactam compounds on cysteine proteases

Example No.	IC_{50} (μ M)	
	Cathepsin B	Cathepsin L
1	>50	26.7
2	>50	>50
3	>50	43.09
4	>50	11.39

	5	>50	8.26
	6	>50	12.08
	7	28.57	2.32
	8	16.42	0.0135
5	9	18.85	0.341
	10	7.51	0.057
	11	0.9	0.015
	12A	0.38	0.003
	12B	0.08	0.0004
10	13A	1.8	0.0029
	13B	0.0715	0.00011
	14A	1.7	0.0027
	14B	0.34	0.0005
	15	1.91	0.0061
15	16	1.6	0.0086
	17	10.1	0.4
	18	1.92	0.0767
	19	1.95	0.39
	20	0.395	0.079
20	21	2.2	0.01
	22	8.4	0.013
	23	11.0	11.5
	24	31.4	0.0168
	25	11	2.19
25	26	>50	10.65
	27	23	2.3
	28	45	11.43
	29	>50	>50
	30	48	1.6
30	31	9.7	0.08

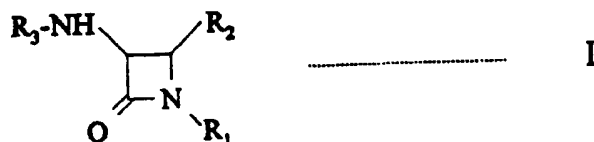
Although the compounds and compositions, and methods of making

and administering them in accordance with the present invention have been described in connection with preferred embodiments, it will be appreciated by those skilled in the art that modifications not specifically described may be made without departing from the spirit and scope of the invention defined in

5 the following claims.

WE CLAIM:

1. A 3,4-disubstituted-azetidin-2-one compound of formula I, or a pharmaceutically acceptable salt thereof:



5 wherein

R_1 is

hydrogen; or

$-SO_3M^+$ wherein M is a hydrogen atom, a metal ion which is selected from sodium, potassium, magnesium, and calcium, or $N^+(R_4)_4$

10 wherein R_4 is a C_1 - C_6 alkyl group;

R_2 is

(a) a group $-OCOR_5$ wherein R_5 is

(i) a C_1 - C_6 alkyl group,

(ii) a C_2 - C_6 alkenyl group,

15 (iii) a C_2 - C_6 alkynyl group,

(iv) a C_3 - C_6 cycloalkyl group,

(v) a phenyl group,

(vi) a naphthyl group, or

(vii) a monocyclic or bicyclic heterocyclic group,

20 which group (i), (ii), (iii), (iv), (v), (vi), or (vii) is unsubstituted or substituted by 1, 2 or 3 substituents independently selected from

hydroxy,

halogen,

25 carboxy,

C₁-C₄ alkyl (which is unsubstituted or substituted at least once with carboxy and/or amino),

C₁-C₂ alkoxy,

amino,

5

cyano, and

phenyl and monocyclic or bicyclic heterocyclic groups, which phenyl and heterocyclic groups are unsubstituted or substituted by 1 or 2 substituents independently selected from

hydroxy,

10

halogen,

carboxy,

C₁-C₄ alkyl,

C₁-C₂ alkoxy,

amino, and

15

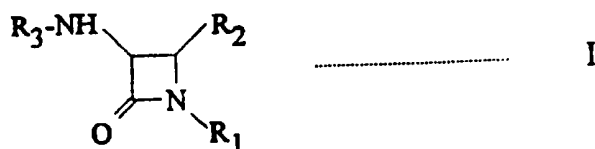
cyano;

or (b) a group -XR₅ wherein X is selected from the group consisting of O, S, SO, and SO₂, and R₅ is as defined above;

R₃ is selected from the group consisting of D- or L-phenyl glycine, D- or L-t-butyl alanine, D- or L-homophenyl alanine, D- or L-pyridyl alanine, D- or L-thienyl alanine, D- or L-naphthyl alanine, D- or L-methoxy phenyl alanine, D- or L-halo phenyl alanine, D- or L-ε-nitro arginine, D- or L-citrulline, D- or L-2-indoline carboxylic acid, D- or L-cycloalkyl glycine (e.g., cyclopentyl glycine), D- or L-4-hydroxy-3-nitro-phenylalanine, D- or L-4-amino-3,5-diiodo-phenylalanine, D- or L-4-hydroxy-3,5-diiodo-phenylalanine, D- or L-4-hydroxy-3,5-dibromo-phenylalanine, D- or L-β-(3-benzothieryl)-alanine, D- or L-3,4(methylenedioxy)phenylalanine, D- or L-3,4(ethylenedioxy)phenylalanine, D- or L-4,4'-biphenylalanine, D- or L-3,4-dichlorophenylalanine, D- or L-4-iodophenylalanine, D- or L-4-nitrophenylalanine, D- or L-pentafluorophenylalanine, D- or L-4-thiazolylalanine, D- or L-3-trifluoromethylphenylalanine, D- or L-4-trifluoromethylphenylalanine, D- or L-3-sulfamoyl-alanine, D- or L-t-butyloxy alanine, D- or L-1-t-butyloxymethylalanine, D- or L-trimethylalanine, D- or L-3,4-

diisopropoxyphenylalanine, D- or L-propyl alanine, and D- or L-ethyl alanine, in which the NH_2 of any of the above groups is unsubstituted or substituted once or twice with R_7 wherein R_7 is $-\text{COOR}_5$, $-\text{COR}_5$, $-\text{SO}_2\text{R}_5$, or $-\text{COR}_{14}$ wherein R_5 is as defined above and R_{14} is amino group which is unsubstituted or substituted at least once with $\text{C}_1\text{-C}_6$ alkyl group which is unsubstituted or substituted at least once with 1 or 2 substituents selected from hydroxy, halogen, cyano, amino, heterocycle, and phenyl (wherein the heterocycle or phenyl is unsubstituted or substituted at least once by 1 or 2 substituents selected from halogen, hydroxy, cyano, carboxy and amino).

2. A 3,4-disubstituted-azetidin-2-one compound of formula I, or a pharmaceutically acceptable salt thereof:



wherein

R_1 is

hydrogen; or

$-\text{SO}_3^-\text{M}^+$ wherein M is a hydrogen atom, a metal ion which is selected from sodium, potassium, magnesium, and calcium, or $\text{N}^+(\text{R}_4)_4$ wherein R_4 is a $\text{C}_1\text{-C}_6$ alkyl group;

R_2 is

$-\text{OCOR}_5$ wherein R_5 is (i) a $\text{C}_1\text{-C}_6$ alkyl group which is unsubstituted or substituted at least once by 1 or 2 substituents selected from hydroxy, halogen, and amino, or (ii) a phenyl group which is unsubstituted or substituted at least once by 1-3 substituents selected from hydroxy, halogen, $\text{C}_1\text{-C}_4$ alkyl group, $\text{C}_1\text{-C}_2$ alkoxy group, and cyano; or

$-\text{XR}_6$ wherein X is O , S , SO , or SO_2 ; R_6 is (i) a $\text{C}_1\text{-C}_6$ alkyl group which is unsubstituted or substituted at least once by 1 or 2 substituents selected from hydroxy, halogen, amino and phenyl (ii) a $\text{C}_3\text{-C}_6$ cycloalkyl

group, (iii) a phenyl group which is unsubstituted or substituted at least once by 1-3 substituents selected from hydroxy, halogen, carboxy, C₁-C₄ alkyl group (which is unsubstituted or substituted with carboxy, amino or both), C₁-C₂ alkoxy group, cyano and heterocycle group, or (iv) naphthyl group which

5 is unsubstituted or substituted at least once by 1-3 substituents selected from hydroxy, halogen, carboxy, C₁-C₄ alkyl group (which is unsubstituted or substituted at least once with carboxy, amino or both), C₁-C₂ alkoxy group and cyano;

R₃ is selected from the group consisting of D- or L-phenyl glycine, D- or L-t-butyl alanine, D- or L-homophenyl alanine, D- or L-pyridyl alanine, D- or L-thienyl alanine, D- or L-naphthyl alanine, D- or L-methoxy phenyl alanine, D- or L-halo phenyl alanine, D- or L-ε-nitro arginine, D- or L-citrulline, D- or L-2-indoline carboxylic acid, D- or L-cycloalkyl glycine (e.g., cyclopentyl glycine), D- or L-4-hydroxy-3-nitro-phenylalanine, D- or L-4-amino-3,5-diiodo-phenylalanine, D- or L-4-hydroxy-3,5-diiodo-phenylalanine, D- or L-4-hydroxy-3,5-dibromo-phenylalanine, D- or L-β-(3-benzothienyl)-alanine, D- or L-3,4(methylenedioxy)phenylalanine, D- or L-3,4(ethylenedioxy)phenylalanine, D- or L-4,4'-biphenylalanine, D- or L-3,4-dichlorophenylalanine, D- or L-4-iodophenylalanine, D- or L-4-nitrophenylalanine, D- or L-pentafluorophenylalanine, D- or L-4-thiazolylalanine, D- or L-3-trifluoromethylphenylalanine, D- or L-4-trifluoromethylphenylalanine, D- or L-3-sulfamoyl-alanine, D- or L-t-butyloxy alanine, D- or L-1-t-butyloxymethylalanine, D- or L-trimethylalanine, D- or L-3,4-diisopropoxyphenylalanine, D- or L-propyl alanine, and D- or L-ethyl alanine,

25 in which the NH₂ of any of the above groups is unsubstituted or substituted once or twice with R₇ wherein R₇ is

-COOR₈ wherein R₈ is a C₁-C₆ alkyl group which is unsubstituted or substituted at least once with phenyl group,

-COR₉ wherein R₉ is

30 (i) a C₁-C₆ alkyl group which is unsubstituted or substituted at least once by 1 or 2 substituents selected from hydroxy, halogen, cyano, amino, heterocycle, or phenyl (wherein the heterocycle or phenyl is

unsubstituted or substituted at least once by 1 or 2 substituents selected from halogen, hydroxy, cyano, carboxy and amino); (ii) a heterocycle which may be mono or bicyclic or (iii) amino group which is unsubstituted or substituted at least once with C₁-C₆ alkyl group which is unsubstituted or substituted at least once with 1 or 2 substituents selected from hydroxy, halogen, cyano, amino, heterocycle, and phenyl (wherein the heterocycle or phenyl is unsubstituted or substituted at least once by 1 or 2 substituents selected from halogen, hydroxy, cyano, carboxy and amino); or

SO₂R₁₀ wherein R₁₀ is

(i) a C₁-C₆ alkyl group (ii) a C₂-C₄ alkenyl group which is unsubstituted or substituted at least once with heterocycle or phenyl, or (iii) a phenyl group which is unsubstituted or substituted at least once by 1-3 substituents selected from hydroxy, halogen, carboxy, C₁-C₄ alkyl group, C₁-C₂ alkoxy group and cyano.

3. A compound or salt as recited in claim 1 or claim 2, wherein R₁ is selected from hydrogen and sulphonic acid.

4. A compound or salt as recited in claim 1 or claim 2, wherein R₂ is selected from acetoxy, butyloxy, 2-carboxy ethyloxy, 2-aminoethyloxy, 2-fluoro ethoxy, cyclopentyloxy, cyclohexyloxy, cyclohexylthio, phenoxy, methyl phenoxy, naphthyloxy, morpholino phenyloxy, 2-hydroxy ethylthio, phenylthio, phenylsulphonyl, 4-(2-carboxy-2-amino ethyl)-phenoxy, 4-carboxy phenoxy, 3-carboxy phenoxy, 2-pyridylthio, 4-pyridylthio, and benzyloxy.

5. A compound or salt as recited in claim 1 or claim 2, wherein R₃ is selected from the group consisting of 1-benzyloxycarbonyl-2-indoline carboxylic acid, N-benzyloxy carbonyl phenyl glycine, N-benzyloxy carbonyl homophenyl alanine, N-benzyloxy carbonyl pyridyl alanine, N-benzyloxy carbonyl thienyl alanine, N-benzyloxy carbonyl naphthyl alanine, N-benzyloxy carbonyl halophenyl alanine, N-benzyloxy carbonyl naphthyl alanine, N-(3-phenyl propanoyl) naphthyl alanine, N^ε-nitro arginine, N-(3-phenyl propanoyl) citrulline, N-benzylamino carbonyl naphthyl alanine, N-(2-phenyl-eth-1-en-sulphonyl)-naphthyl alanine, N-benzyloxycarbonyl-t-butyloxyalanine; N-benzyloxycarbonyl-t-butyloxymethyl alanine; N-benzyloxycarbonyl-t-butyl

alanine; N-phenylpropionoyl-t-butyl alanine; N-phenylpropionoyl-trimethyl
alanine; N-phenylpropionoyl-(3, 4-dimethoxyphenyl) alanine; N-
phenylpropionoyl-(3,4-ethylenedioxyphenyl) alanine; N-benzyloxycarbonyl-3-
benzothienyl alanine; N-benzyloxycarbonyl-(4,4'-biphenyl) alanine; N-
5 benzyloxycarbonyl-(2-chlorophenyl)alanine; N-benzyloxycarbonyl-(4-
chlorophenyl)alanine; N-benzyloxycarbonyl-(3,4-dichloro)-phenylalanine; N-
benzyloxycarbonyl-(diphenyl) alanine; N-benzyloxycarbonyl-(2-fluoro)
phenylalanine; N-benzyloxycarbonyl-(4-fluoro-phenyl) alanine; N-
benzyloxycarbonyl-(3,4-difluoro-phenyl) alanine; N-benzyloxycarbonyl-(4-
10 iodo-phenyl) alanine; N-benzyloxycarbonyl-2-(naphthyl) alanine; N-
benzyloxycarbonyl-(4-nitro-phenyl) alanine; N-benzyloxycarbonyl-
(pentafluorophenyl) alanine; N-benzyloxycarbonyl-(4-thiazolyl) alanine; N-
benzyloxycarbonyl-3-(trifluoromethylphenyl) alanine; N-benzyloxycarbonyl-4-
(trifluoromethylphenyl) alanine; N-benzyloxycarbonyl-(3-sulfamoyl) alanine;
15 N-phenylpropionoyl-(3,4-methylenedioxyphenyl) alanine; N-phenylpropionoyl-
(3,4-diisopropoxyphenyl) alanine; N-benzyloxycarbonyl-propyl alanine; and
N-benzyloxycarbonyl-ethyl alanine.

6. A compound or salt as recited in claim 1 or claim 2, having (3R,4S),
(3R,4R), (3S,4R) or (3S,4S) configuration at two asymmetric carbons 3 and
20 4 on azetidin-2-one ring system or a racemic mixture thereof.

7. A compound or salt as recited in claim 1 or claim 2, wherein said
unnatural amino acid residue is a D isomer, an L isomer, or a racemic mixture
thereof.

8. A compound or salt as recited in claim 1 or claim 2, wherein said
25 substituent group is selected from the group consisting of aryloxy carbonyl,
alkoxy carbonyl, substituted alkanoyl, arylalkanoyl, arylalkenoyl,
heterocyclealkenoyl, heterocyclealkanoyl, alkylsulphonyl, arylsulphonyl,
arylalkanylsulphonyl, arylalkensulphonyl, heterocyclealkanylsulphonyl,
heterocyclealkensulphonyl, and heterocyclesulphonyl.

9. A salt as recited in claim 1 or claim 2, wherein said salt comprises
30 a component selected from sodium, potassium, magnesium, calcium,
hydrogen chloride, tartaric acid, succinic acid, fumaric acid and p-

toluenesulfonic acid.

10. A pharmaceutical composition comprising a compound or salt as recited in claim 1 or claim 2 and a pharmaceutically acceptable carrier.

5 11. A method of treatment of muscular dystrophy, comprising administering to a patient in need of said treatment a pharmaceutical composition comprising a compound or salt as recited in claim 1 or claim 2 in an amount effective for treating said muscular dystrophy, and a pharmaceutically acceptable carrier.

10 12. A method of treatment of cancer metastasis, comprising administering to a patient in need of said treatment a pharmaceutical composition comprising a compound or salt as recited in claim 1 or claim 2 in an amount effective for treating said cancer metastasis, and a pharmaceutically acceptable carrier.

15 13. A method of treatment of myocardial infarction, comprising administering to a patient in need of said treatment a pharmaceutical composition comprising a compound or salt as recited in claim 1 or claim 2 in an amount effective for treating said myocardial infarction, and a pharmaceutically acceptable carrier.

20 14. A method of treatment of inflammatory disease in a patient in need of such treatment, comprising administering to said patient a pharmaceutical composition comprising a compound or salt as recited in claim 1 or claim 2 in an amount which is effective for treating inflammatory disease, and a pharmaceutically acceptable carrier.

25 15. A method of treatment of arthritis in a patient in need of such treatment, comprising administering to said patient a pharmaceutical composition comprising a compound or salt as recited in claim 1 or claim 2 in an amount which is effective for treating arthritis, and a pharmaceutically acceptable carrier.

30 16. A method of treatment of pulmonary emphysema in a patient in need of such treatment, comprising administering to said patient a pharmaceutical composition comprising a compound or salt as recited in claim 1 or claim 2 in an amount which is effective for treating pulmonary

emphysema, and a pharmaceutically acceptable carrier.

17. A method of treatment of septic shock in a patient in need of such treatment, comprising administering to said patient a pharmaceutical composition comprising a compound or salt as recited in claim 1 or claim 2 in
5 an amount which is effective for treating septic shock, and a pharmaceutically acceptable carrier.

18. A method of treatment of cerebral ischemia in a patient in need of such treatment, comprising administering to said patient a pharmaceutical composition comprising a compound or salt as recited in claim 1 or claim 2 in
10 an amount which is effective for treating cerebral ischemia, and a pharmaceutically acceptable carrier.

19. A method for improvement of memory function in a patient in need of such improvement, comprising administering to said patient a pharmaceutical composition comprising a compound or salt as recited in claim
15 1 or claim 2 in an amount which is effective for improving memory function, and a pharmaceutically acceptable carrier.

20. A method of treatment of parasitic infection in a patient in need of such treatment, comprising administering to said patient a pharmaceutical composition comprising a compound or salt as recited in claim 1 or claim 2 in
20 an amount which is effective for treating parasitic infection, and a pharmaceutically acceptable carrier.

21. A method of treatment of cataract in a patient in need of such treatment, comprising administering to said patient a pharmaceutical composition comprising a compound or salt as recited in claim 1 or claim 2 in
25 an amount which is effective for treating cataract, and a pharmaceutically acceptable carrier.

22. A method of treatment of malaria in a patient in need of such treatment, comprising administering to said patient a pharmaceutical composition comprising a compound or salt as recited in claim 1 or claim 2 in
30 an amount which is effective for treating malaria, and a pharmaceutically acceptable carrier.

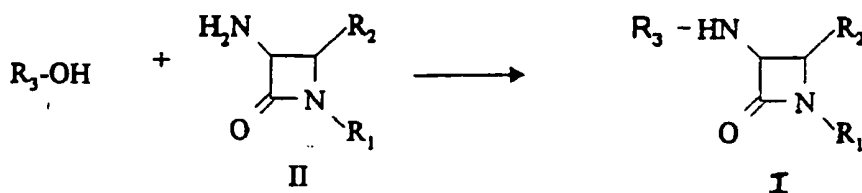
23. A method of treatment of glomerular basement membrane degradation in a patient in need of such treatment, comprising administering to said patient a pharmaceutical composition comprising a compound or salt as recited in claim 1 or claim 2 in an amount which is effective for treating
 5 glomerular basement membrane degradation, and a pharmaceutically acceptable carrier.

24. A method of treatment of viral infection in a patient in need of such treatment, comprising administering to said patient a pharmaceutical composition comprising a compound or salt as recited in claim 1 or claim 2 in
 10 an amount which is effective for treating viral infection, and a pharmaceutically acceptable carrier.

25. A method of regulating cysteine protease in a patient in need of such regulating, comprising administering to said patient a pharmaceutical composition comprising a compound or salt as recited in claim 1 or claim 2 in
 15 an amount which is effective for treating regulating cysteine protease, and a pharmaceutically acceptable carrier.

26. A method of treatment of osteoporosis, comprising administering to a patient in need of said treatment a pharmaceutical composition comprising a compound or salt as recited in claim 1 or claim 2 in an amount
 20 effective for treating said osteoporosis, and a pharmaceutically acceptable carrier.

27. A method of preparing a compound of formula I, comprising reacting a compound according to formula II with a compound of the formula R_3 -OH acid in presence of at least one member selected from the group consisting of dicyclohexylcarbodiimide and acid chloride in the presence of at
 25 least one member selected from the group consisting of base and activated ester:



wherein

R_1 is

hydrogen; or

$-SO_3M^+$ wherein M is a hydrogen atom, a metal ion which is

5 selected from sodium, potassium, magnesium, and calcium, or $N^+(R_4)_4$

wherein R_4 is a C_1 - C_6 alkyl group;

R_2 is

(a) a group $-OCOR_5$ wherein R_5 is

(i) a C_1 - C_6 alkyl group,

10 (ii) a C_2 - C_6 alkenyl group,

(iii) a C_2 - C_6 alkynyl group,

(iv) a C_3 - C_6 cycloalkyl group,

(v) a phenyl group,

(vi) a naphthyl group, or

15 (vii) a monocyclic or bicyclic heterocyclic group,

which group (i), (ii), (iii), (iv), (v), (vi), or (vii) is

unsubstituted or substituted by 1, 2 or 3

substituents independently selected from

hydroxy,

20 halogen,

carboxy,

C_1 - C_4 alkyl (which is unsubstituted or
substituted at least once with carboxy and/or amino),

C_1 - C_2 alkoxy,

25 amino,

cyano, and

phenyl and monocyclic or bicyclic
heterocyclic groups, which phenyl and heterocyclic groups are unsubstituted
or substituted by 1 or 2 substituents independently selected from

30 hydroxy,

halogen,

carboxy,

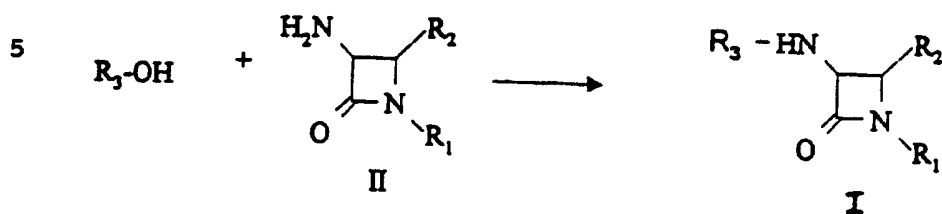
C₁-C₄ alkyl,
 C₁-C₂ alkoxy,
 amino, and
 cyano;

5 or (b) a group -XR₅ wherein X is selected from the group consisting of O, S, SO, and SO₂, and R₅ is as defined above;

R₃ is selected from the group consisting of D- or L-phenyl glycine, D- or L-t-butyl alanine, D- or L-homophenyl alanine, D- or L-pyridyl alanine, D- or L-thienyl alanine, D- or L-naphthyl alanine, D- or L-methoxy phenyl alanine,
 10 D- or L-halo phenyl alanine, D- or L-ε-nitro arginine, D- or L-citrulline, D- or L-2-indoline carboxylic acid, D- or L-cycloalkyl glycine (e.g., cyclopentyl glycine), D- or L-4-hydroxy-3-nitro-phenylalanine, D- or L-4-amino-3,5-diiodo-phenylalanine, D- or L-4-hydroxy-3,5-diiodo-phenylalanine, D- or L-4-hydroxy-3,5-dibromo-phenylalanine, D- or L-β-(3-benzothieryl)-alanine, D- or L-3,4(methylenedioxy)phenylalanine, D- or L-3,4(ethylenedioxy)phenylalanine,
 15 D- or L-4,4'-biphenylalanine, D- or L-3,4-dichlorophenylalanine, D- or L-4-iodophenylalanine, D- or L-4-nitrophenylalanine, D- or L-pentafluorophenylalanine, D- or L-4-thiazolylalanine, D- or L-3-trifluoromethylphenylalanine, D- or L-4-trifluoromethylphenylalanine, D- or L-3-sulfamoyl-alanine, D- or L-t-butyloxy alanine, D- or L-1-t-butyloxymethylalanine, D- or L-trimethylalanine, D- or L-3,4-diisopropoxyphenylalanine, D- or L-propyl alanine, and D- or L-ethyl alanine, in which the NH₂ of any of the above groups is unsubstituted or substituted once or twice with R₇ wherein R₇ is -COOR₅, -COR₅, -SO₂R₅, or -COR₁₄
 25 wherein R₅ is as defined above and R₁₄ is amino group which is unsubstituted or substituted at least once with C₁-C₆ alkyl group which is unsubstituted or substituted at least once with 1 or 2 substituents selected from hydroxy, halogen, cyano, amino, heterocycle, and phenyl (wherein the heterocycle or phenyl is unsubstituted or substituted at least once by 1 or 2
 30 substituents selected from halogen, hydroxy, cyano, carboxy and amino).

28. A method of preparing a compound of formula I, comprising reacting a compound according to formula II with a compound of the formula

R_3 -OH acid in presence of at least one member selected from the group consisting of dicyclohexylcarbodiimide and acid chloride in the presence of at least one member selected from the group consisting of base and activated ester:



wherein

R_1 is

hydrogen; or

$-SO_3^-M^+$ wherein M is a hydrogen atom, a metal ion which is selected from sodium, potassium, magnesium, and calcium, or $N^+(R_4)_4$

wherein R_4 is a C_1 - C_6 alkyl group;

R_2 is

$-OCOR_5$ wherein R_5 is (i) a C_1 - C_6 alkyl group which is unsubstituted or substituted at least once by 1 or 2 substituents selected from hydroxy, halogen, and amino, or (ii) a phenyl group which is unsubstituted or substituted at least once by 1-3 substituents selected from hydroxy, halogen, C_1 - C_4 alkyl group, C_1 - C_2 alkoxy group, and cyano; or

$-XR_6$ wherein X is O, S, SO, or SO_2 ; R_6 is (i) a C_1 - C_6 alkyl group which is unsubstituted or substituted at least once by 1 or 2 substituents selected from hydroxy, halogen, amino and phenyl (ii) a C_3 - C_6 cycloalkyl group, (iii) a phenyl group which is unsubstituted or substituted at least once by 1-3 substituents selected from hydroxy, halogen, carboxy, C_1 - C_4 alkyl group (which is unsubstituted or substituted with carboxy, amino or both), C_1 - C_2 alkoxy group, cyano and heterocycle group, or (iv) naphthyl group which is unsubstituted or substituted at least once by 1-3 substituents selected from hydroxy, halogen, carboxy, C_1 - C_4 alkyl group (which is unsubstituted or

substituted at least once with carboxy, amino or both), C_1 - C_2 alkoxy group and cyano;

R_3 is selected from the group consisting of D- or L-phenyl glycine, D- or L-t-butyl alanine, D- or L-homophenyl alanine, D- or L-pyridyl alanine, D- or L-thienyl alanine, D- or L-naphthyl alanine, D- or L-methoxy phenyl alanine, D- or L-halo phenyl alanine, D- or L-e-nitro arginine, D- or L-citrulline, D- or L-2-indoline carboxylic acid, D- or L-cycloalkyl glycine (e.g., cyclopentyl glycine), D- or L-4-hydroxy-3-nitro-phenylalanine, D- or L-4-amino-3,5-diiodo-phenylalanine, D- or L-4-hydroxy-3,5-diiodo-phenylalanine, D- or L-4-hydroxy-3,5-dibromo-phenylalanine, D- or L- β -(3-benzothienyl)-alanine, D- or L-3,4(methylenedioxy)phenylalanine, D- or L-3,4(ethylenedioxy)phenylalanine, D- or L-4,4'-biphenylalanine, D- or L-3,4-dichlorophenylalanine, D- or L-4-iodophenylalanine, D- or L-4-nitrophenylalanine, D- or L-pentafluorophenylalanine, D- or L-4-thiazolylalanine, D- or L-3-trifluoromethylphenylalanine, D- or L-4-trifluoromethylphenylalanine, D- or L-3-sulfamoyl-alanine, D- or L-t-butyloxy alanine, D- or L-1-t-butyloxymethylalanine, D- or L-trimethylalanine, D- or L-3,4-diisopropoxyphenylalanine, D- or L-propyl alanine, and D- or L-ethyl alanine, in which the NH_2 of any of the above groups is unsubstituted or substituted once or twice with R_7 wherein R_7 is

- $COOR_8$ wherein R_8 is a C_1 - C_6 alkyl group which is unsubstituted or substituted at least once with phenyl group,

- COR_9 wherein R_9 is

(i) a C_1 - C_6 alkyl group which is unsubstituted or substituted at least once by 1 or 2 substitutents selected from hydroxy, halogen, cyano, amino, heterocycle, or phenyl (wherein the heterocycle or phenyl is unsubstituted or substituted at least once by 1 or 2 substituents selected from halogen, hydroxy, cyano, carboxy and amino); (ii) a heterocycle which may be mono or bicyclic or (iii) amino group which is unsubstituted or substituted at least once with C_1 - C_6 alkyl group which is unsubstituted or substituted at least once with 1 or 2 substitutents selected from hydroxy, halogen, cyano, amino, heterocycle, and phenyl (wherein the heterocycle or phenyl is unsubstituted

or substituted at least once by 1 or 2 substituents selected from halogen, hydroxy, cyano, carboxy and amino); or

SO₂R₁₀ wherein R₁₀ is

- (i) a C₁-C₆ alkyl group (ii) a C₂-C₄ alkenyl group which is
5 unsubstituted or substituted at least once with heterocycle or phenyl, or (iii)
a phenyl group which is unsubstituted or substituted at least once by 1-3
substituents selected from hydroxy, halogen, carboxy, C₁-C₄ alkyl group, C₁-
C₂ alkoxy group and cyano.

29. A compound selected from the group consisting of:

- 10 (3S,4S)-3-(1-N-benzyloxycarbonyl-2-indolinecarbonyl)-amino-4 -
acetoxo-azetidin-2-one;

(3S,4S)-3-(N-benzyloxycarbonyl-D-phenylglycyl)-amino-4-acetoxo-
azetidin-2-one;

- (3S,4S)-3-(N-benzyloxycarbonyl-DL-phenylglycyl)-amino-4-acetoxo-
15 azetidin-2-one;

(3S,4S)-3-(N-benzyloxycarbonyl-L-homophenylalanyl)-amino-4 -
acetoxo-azetidin-2-one;

(3S,4S)-3-{N-benzyloxycarbonyl-β-(3-pyridyl)-L-alanyl}-amino-4 -
acetoxo-azetidin-2-one;

- 20 (3S,4S)-3-{N-benzyloxycarbonyl-β-(2-pyridyl)-L-alanyl}-amino-4 -
acetoxo-azetidin-2-one;

(3S,4S)-3-{N-benzyloxycarbonyl-β-(2-thienyl)-DL-alanyl}-amino-4-
acetoxo-azetidin-2-one;

- (3S,4S)-3-{N-benzyloxycarbonyl-β-(2-naphthyl)-L-alanyl}-amino-4-
25 acetoxo-azetidin-2-one;

(3S,4S)-3-{N-benzyloxycarbonyl-β-(3-fluorophenyl)-L-alanyl}-amino-4-
acetoxo-azetidin-2-one;

(3S,4S)-3-{N-benzyloxycarbonyl-β-(4-methoxyphenyl)-L-alanyl}-amino-
4-acetoxo-azetidin-2-one;

- 30 (3S,4S)-3-{N-benzyloxycarbonyl-β-(2-naphthyl)-L-alanyl}-amino-4-
phenoxy-azetidin-2-one;

(3S,4S)-3-{N-benzyloxycarbonyl-β-(2-naphthyl)-L-alanyl}-amino-4-(3-

- methyl phenoxy)-azetidin-2-one;
(3S,4R)-3-{N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl}-amino-4-(3-methyl phenoxy)-azetidin-2-one;
(3S,4S)-3-{N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl}-amino-4-(2-naphthoxy)-azetidin-2-one;
5 (3S,4R)-3-{N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl}-amino-4-(2-naphthoxy)-azetidin-2-one;
(3S,4S)-3-{N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl}-amino-4-{3-(morpholin-4-yl)-phenoxy}-azetidin-2-one;
10 (3S,4R)-3-{N-benzyloxycarbonyl- β -(2-naphthyl)-L-alanyl}-amino-4-{3-(morpholin-4-yl)-phenoxy}-azetidin-2-one;
(3S,4SR)-3-{N-(3-phenylpropionoyl)- β -(2-naphthyl)-L-alanyl}-amino-4-phenylthio-azetidin-2-one;
(3S,4SR)-3-{N-(3-phenylpropionoyl)- β -(2-naphthyl)-L-alanyl}-amino-4-phenylsulphonyl-azetidin-2-one;
15 (3S,4SR)-3-{N-(3-phenylpropionoyl)- β -(2-naphthyl)-L-alanyl}-amino-4-(2-hydroxy ethyl thio)-azetidin-2-one;
(3S,4SR)-3-{N-(3-phenylpropionoyl)- β -(2-naphthyl)-L-alanyl}-amino-4-benzyloxy-azetidin-2-one;
20 (3S,4SR)-3-{N-(3-phenylpropionoyl)- β -(2-naphthyl)-L-alanyl}-amino-4-cyclohexyloxy-azetidin-2-one;
(3S,4S)-3-{N-(trans-2-phenyl-eth-1-enesulfonyl)- β -(2-naphthyl)-L-alanyl}-amino-4-acetoxy-azetidin-2-one;
(3S,4SR)-3-{N-(3-phenylpropionoyl)- β -(2-naphthyl)-L-alanyl}-amino-4-{4-(2S-2-amino-2-carboxyethyl)-phenoxy}-azetidin-2-one;
25 (3S,4S)-3-{N-(benzylaminocarbonyl)- β -(2-naphthyl)-L-alanyl}-amino-4-acetoxy-azetidin-2-one;
(3S,4SR)-3-{N-(benzylaminocarbonyl)- β -(2-naphthyl)-L-alanyl}-amino-4-{4-(2S-2-amino-2-carboxyethyl)-phenoxy}-azetidin-2-one;
30 (3S,4S)-3-{N-(3-phenylpropionoyl)-L-citrullinyl}-amino-4-acetoxy-azetidin-2-one;
(3S,4S)-3-{N-(2-phenyl-eth-1-en-sulphonyl)- β -(2-naphthyl)-L-alanyl}-

- amino-4-acetoxy-azetidin-2-one;
(3S,4S)-3-{N^α-(3-phenylpropionyl)-N^ε-nitro-L-arginyl}-
amino-4-acetoxy-azetidin-2-one;
(3S,4R)-3-(2S-2-benzyloxycarbonylamino-2-t-butyloxymethyl -
5 acetamido)-4-phenoxy-azetidin-2-one;
(3S,4R)-3-[2S-2-benzyloxycarbonylamino-2-(1-t-butyloxyethyl)-
acetamido]-4-phenoxy-azetidin-2-one;
(3S, 4S)-3-(2S-2-benzyloxycarbonylamino-2-t-butylmethyl-acetamido)-
4-phenoxy-azetidin-2-one;
10 (3S,4S)-3-[2S-2-(3-phenylpropionoyl)amino-2-t-butylmethyl-acetamido]-
4-phenoxy-azetidin-2-one;
(3S,4S)-3-[2S-2-(3-phenylpropionoyl)amino-2-t-butyl-acetamido]-4-
phenoxy-azetidin-2-one;
(3S,4S)-3-[2S-2-(3-phenylpropionoyl) amino-2-(3, 4-dimethoxyphenyl)
15 methyl- acetamido]-4-phenoxy-azetidin-2-one;
(3S, 4S) -3-[2S-3-phenylpropionoyl) amino-2-(3,4-
ethylenedioxyphenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one;
(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(3-benzothienylmethyl)-
acetamido]-4-phenoxy-azetidin-2-one;
20 (3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(4,4'-biphenylmethyl)-
acetamido]-4-phenoxy-azetidin-2-one;
(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(2-chloro-phenylmethyl)-
acetamido]-4-phenoxy-azetidin-2-one;
(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(4-chloro-phenylmethyl)-
25 acetamido]-4-phenoxy-azetidin-2-one;
(3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(3,4-dichloro -
phenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one;
(3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(diphenylmethyl) -
acetamido]-4-phenoxy-azetidin-2-one;
30 (3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(2-fluoro-phenylmethyl)-
acetamido]-4-phenoxy-azetidin-2-one;
(3S, 4S)-3-[2S-2-benzyloxycarbonylamino-2-(4-fluoro-phenylmethyl)-

- acetamido]-4-phenoxy-azetidin-2-one;
(3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(3,4-difluoro -
phenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one;
(3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(4-iodo-phenylmethyl)-
5 acetamido]-4-phenoxy-azetidin-2-one;
(3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(naphth-1-yl)methyl -
acetamido]-4-phenoxy-azetidin-2-one;
(3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(4-nitro-phenylmethyl)-
acetamido]-4-phenoxy-azetidin-2-one;
10 (3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(pentafluorophenyl -
methyl)-acetamido]-4-phenoxy-azetidin-2-one;
(3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(4-thiazolylmethyl)-
acetamido]-4-phenoxy-azetidin-2-one;
(3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(3-trifluoromethylphenyl-
15 methyl)-acetamido]-4-phenoxy-azetidin-2-one;
(3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-(3-sulfamoylmethyl) -
acetamido]-4-phenoxy-azetidin-2-one;
(3S,4S)-3-[2S-2-(3-phenylpropionoyl) amino-2-(3,4-
methylenedioxyphenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one;
20 (3S,4S)-3-[2S-2-(3-phenylpropionoyl) amino-2-(3,4-
diisopropoxyphenylmethyl)-acetamido]-4-phenoxy-azetidin-2-one;
(3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-butyl-acetamido]-4-
phenoxy-azetidin-2-one; and
(3S,4S)-3-[2S-2-benzyloxycarbonylamino-2-propyl-acetamido]-4 -
25 phenoxy-azetidin-2-one,
and salts thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/IB 97/01145		
A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D205/085 A61K31/395		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 96 32408 A (SYNPHAR LABORATORIES, INC.) 17 October 1996 cited in the application see claims 1,7,14,20 ---	1,2,10, 27,28
A	EP 0 053 815 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 16 June 1982 see page 14, line 1 - line 11; claims 1,2,16 ---	1-3,10
A	EP 0 053 816 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 16 June 1982 see page 15, line 19 - line 24; claims 1,35,67 --- -/--	1-3,10
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search 16 December 1997		Date of mailing of the international search report 07. 01. 98
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Hass, C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 97/01145

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 093 376 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 9 November 1983 see page 11, line 34 - page 12, line 10 see page 15, line 19 - line 24; claims 1,34 ---	1-3,10
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A	EP 0 050 965 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 5 May 1982 see page 11, line 26 - line 35; claims 1,3 ---	1-3,10
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 97/01145

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 11-26

because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Remark : Although claims 11-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 97/01145

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Information on patent family members

International Application No

PCT/IB 97/01145

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